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TUBERCULOUS MENINGITIS OF ACUTE ONSET

BY

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The classical descriptions of tuberculous meningitis all emphasize the insidious onset as one of the chief characteristics of the disease. Modern experience has amply confirmed this. For example, in a series of 55 young Servicemen treated at the Military Hospital for Head Injuries, Wheatley, and for whom a full history was obtained, 43 had been ill for over one week and 15 for over three weeks before admission to hospital (Taylor, 1954). At the same time, we have occasionally seen cases in which the onset, so far from being insidious, has been acute or even abrupt (Smith and Vollum, 1954 ; Case 1). As these cases have accumulated so we have come to recognize that they resemble each other in several respects besides the onset ; in particular, early in the illness the cell counts in the cerebrospinal fluid (C.S.F.) are unusually high ; the symptoms often remit very rapidly, sometimes even before treatment is begun ; on the whole, the prognosis is good.

These cases therefore appear to form a small but definite group within the series as a whole. But, though rare, they are of some importance both because the unusual history and C.S.F. findings tend to confuse the diagnosis, and because they throw some light on the pathogenesis of the C.S.F. changes in tuberculous meningitis in general.

Incidence

In a series of 200 consecutive unselected cases of tuberculous meningitis treated at the Military Hospital for Head Injuries, Wheatley, and at the United Oxford Hospitals, there are eight in which the patients had been ill for less than one week when admitted to hospital and in which the C.S.F. was found to contain 500 cells per c.mm. or more at least once before treatment was begun. A ninth case (Case No. 118), in which the patient died on the tenth day of illness, has been included on clinical grounds, even though the C.S.F. findings were not typical. The diagnosis was confirmed in all cases by identification of *M. tuberculosis* in the C.S.F.

A minimal count of 500 cells per c.mm. was arbitrarily chosen as a criterion for inclusion in this group because it is often accepted as the upper limit for cell counts in tuberculous meningitis (Merritt and Fremont-Smith, 1937). Had the minimum been set a little lower, e.g., at 450 cells per c.mm., a few more cases would have been included. The syndrome under discussion was thus seen in at least 4% of all cases.

The Clinical Picture

The relevant findings in these cases are summarized in Table I. The patients varied in age between 6 and 36 years ; one was female and the rest were males. This apparent sex difference is simply a reflexion of the preponderance of males in the series as a whole, due to the fact that Servicemen as well as civilians are treated at this centre.

In all cases the patients became so rapidly and so obviously unwell that they were admitted to hospital some time during the first week of their illness. The departure from normal health was usually so abrupt that the interval between the onset of symptoms and admission to hospital can be calculated with fair accuracy. Several patients were first admitted to hospitals elsewhere and later transferred to us for diagnosis and treatment, and the day of the disease on which treatment was begun corresponds with the time at which the diagnosis was made.

Table I also shows the stage the disease had reached at the outset of treatment (Medical Research Council Report, 1948). In four cases the disease was still in the " early " stage ; that is to say, the patients were fully conscious and rational and without any focal neurological signs. This might be expected in view of the short histories, but it should be noted that one patient (Case No. 199) had already reached the " intermediate " stage by the eighth day of his illness, while four were already sufficiently delirious or comatose to render them

* Working with a grant from the Medical Research Council.

TABLE I

LENGTH OF ONSET, HIGHEST C.S.F. CELL COUNTS, INCIDENCE OF RAPID REMISSION OF SYMPTOMS, AND OUTCOME IN NINE CASES

Case No.	Sex	Age	Duration of Symptoms		Maximum Cells (C.S.F.) before Treatment	Stage of Disease when Treatment Begun	Rapid Relief of Symptoms	Result
			Before Admission (days)	Before Treatment Begun (days)				
8	M.	18	5	8	500	Early	Yes	Recovered
60	M.	36	6	6	1,600	Late	Yes	Recovered
65	M.	6	7	7	514	Early	Yes	Recovered
89	M.	15	7	21	740	Late	Yes	Died
110	F.	18	2	4	500	Early	Yes	Recovered
168	M.	11	8*	19	1,070	Late	Yes	Recovered
196	M.	19	3	19	1,300	Early	Yes	Recovered
199	M.	27	4	7	890	Intermediate	Yes	Recovered
118	M.	19	1	8	100	Late	No	Died

* Meningitis diagnosed by private doctor on seventh day of illness.

completely inaccessible. In two cases (Nos. 89 and 168) this was due to delay in diagnosis and consequently in the institution of chemotherapy, but in both the others the disease had reached the "advanced" stage by the eighth day, and in one of these (Case No. 118) it ran its full course to death in only 10 days. The other patients recovered completely. The follow-up period for this group varies between one and seven years.

The typical clinical picture is shown by the following case :—

Case No. 196.—A young National Serviceman aged 19 years reported sick on September 8, 1953. He complained that for the past two days he had been feeling unwell, that his back had been stiff, and that he had had a dull, aching pain between the shoulders. On examination he was found to be feverish, but there were no other abnormal physical signs. He was admitted to hospital, and two days later he developed a moderately severe frontal headache. This persisted, and on September 13, just seven days after he first began to feel ill, it was noticed that his neck was stiff. A diagnostic lumbar puncture was therefore performed which yielded a fluid under a pressure of 130 mm. C.S.F. containing 1,300 cells per c.mm., of which 60% were mononuclears. The protein content was 320 mg. per 100 ml., the sugar 60 mg. per 100 ml., and the chloride 760 per 100 ml. In view of the normal sugar and chloride contents, a tentative diagnosis was made of non- or pre-paralytic anterior poliomyelitis, and no chemotherapy was given.

Following the lumbar puncture he improved remarkably : within a few days the temperature had settled and the headache and neck stiffness disappeared. Nevertheless, a second lumbar puncture on September 17 showed that the C.S.F. still contained 1,300 cells per c.mm., of which 90% were mononuclears ; the sugar content was now 45 mg. per 100 ml. and the protein content was unchanged. A third specimen of C.S.F. obtained on September 24 gave essentially similar findings. In view of these persistent abnormalities in the C.S.F., the patient was transferred to the Military Hospital for Head Injuries on September 25.

On admission he looked so well that it was difficult to believe that he had anything seriously wrong with him. He would not admit to any headache or other symptom, and indeed frequently asked why he was being kept in hospital. There were no abnormal physical signs whatever, and, in particular, all movements of the neck were full and painless. Radiography of the chest showed no abnormality, and the Mantoux test was weakly positive to 0·1 ml. old tuberculin 1 in 100. However, in spite of his apparent well-being and the absence of all signs of meningeal irritation, lumbar puncture showed that the C.S.F. still contained 740 cells per c.mm., of which 99% were mononuclears ; the protein content was 560 mg. per 100 ml., and the sugar and chlorides 35 mg. and 670 mg. per 100 ml. respectively.

A provisional diagnosis of tuberculous meningitis of acute onset was made, and treatment with systemic and intrathecal streptomycin and isonicotinic acid hydrazide (I.N.A.H.) was begun immediately. The diagnosis received strong support from the estimation of the partition of bromide between serum and C.S.F. This showed that the ratio was only 1·06, a characteristic finding in tuberculous meningitis (Taylor, Smith, and Hunter, 1954). It was not, however, confirmed until the nineteenth day of treatment, when *M. tuberculosis* was identified in a single specimen of cisternal C.S.F. Later still, *M. tuberculosis* was isolated by culture from the specimen of lumbar C.S.F. obtained on the thirteenth day of treatment.

As soon as bacteriological confirmation of the diagnosis was obtained the daily intrathecal and systemic chemotherapy was supplemented by intermittent intrathecal injections of tuberculin (Smith and Vollum, 1950;

Smith, 1953). The spontaneous remission of symptoms was maintained, and the patient made a rapid and uninterrupted recovery.

This case exemplifies all three features which together form the syndrome under discussion. In the first place, only eight days elapsed between the first departure from normal health and the time when stiffness of the neck became sufficiently obvious to compel lumbar puncture. Secondly, the first three specimens of C.S.F. all contained more than 1,000 cells per c.mm., while even the fourth contained 740 cells per c.mm. In the first specimen, 40% of these cells were polymorphonuclears; thereafter they were virtually all mononuclears. The C.S.F. findings in this case also differed from those typical of tuberculous meningitis in that the sugar and chloride contents at the first three examinations were within the limits of normal. Thirdly, there was a well-marked spontaneous remission of both signs and symptoms. This preceded the institution of chemotherapy by no less than two weeks, in spite of the fact that the meningeal infection remained active, as shown unequivocally by the isolation of *M. tuberculosis* on two separate occasions during the fifth and sixth weeks of the illness. Finally, this early remission led on uninterruptedly to a permanent recovery with appropriate chemotherapy.

Diagnosis

As this case shows, diagnosis can be extremely difficult. This difficulty is reflected by the interval between the patients' first admission to hospital and the time when treatment was begun (Table I). The problem of diagnosis in tuberculous meningitis in general has been discussed elsewhere (Smith and Vollum, 1954), and in this group of cases the differential diagnosis has included acute purulent meningitis and subarachnoid haemorrhage (Cases No. 110 and 60), non-paralytic poliomyelitis (Case No. 196), intracranial haemorrhage and brain abscess (Case No. 168), frontal sinusitis and hysteria (Case No. 8), and benign chorio-lymphocytic meningitis (Cases Nos. 8 and 89). It is this last condition that is perhaps the most confusing, and differentiation is made the more difficult by the tendency in the acute tuberculous cases for symptoms to remit spontaneously. Even when treatment is withheld the patient's improvement may still be such as to appear to clinch the diagnosis in favour of benign chorio-lymphocytic meningitis. The fact that remission is only temporary may then not be appreciated until too late. The following case illustrates the difficulties in diagnosis that may be encountered and the dangers to which the patient may consequently be exposed.

Case No. 8.—This case has already been described by Smith, Vollum, and Cairns (1948, Case 8).

A young aircraftman aged 18 years was transferred from another hospital to the Military Hospital for Head Injuries, Wheatley, on April 26, 1947. Ten days earlier he had felt a little unwell and thought he had caught a cold in his head. Three days later, on April 19, he went home on leave and that same day developed severe frontal headache and a purulent nasal discharge. He went to bed and was treated by his family doctor for acute frontal sinusitis. The nasal discharge cleared up in about three days, but the headache grew steadily worse until it became so intense that it prevented him from sleeping, and indeed at times was almost unbearable. The pain also began to spread down the neck. He began to vomit and became extremely restless.

After five days he was admitted to the Casualty Reception Station belonging to his unit. At this stage he was restless and moaning and plucking at his bedclothes. No clear account of his symptoms could be obtained, but his chief complaints seemed to be giddiness, lack of sleep, and repeated vomiting. He was apyrexial, and no abnormal physical signs were detected. This same day he began to have intermittent attacks of double vision. It was thought that his symptoms were psychogenic, and the next day he was transferred to the Q.A. Military Hospital, Milbank. There he was found to have a temperature of 101° F. and was moaning from the intensity of his headache. There were no other abnormal findings. On lumbar puncture the C.S.F. was found to be under increased pressure and to contain 50 mononuclears per c.mm. The sugar was reduced and the chloride content 635 mg. per 100 ml. He was transferred to us the following day.

On admission he was feverish and looked ill and flushed. Although he was in great distress from his headache, he was able to give a fairly detailed history and to cooperate in a full examination. Except for moderate stiffness of the neck, this showed no abnormality whatever. Radiographs of the chest and skull were normal. Lumbar puncture yielded a fluid under a pressure of well over 300 mm. C.S.F. and containing 600 cells, of which 98% were mononuclears, protein 360 mg. per 100 ml., and chlorides 680 mg. per 100 ml. Not enough C.S.F. was obtained for estimation of the sugar. A provisional diagnosis of tuberculous meningitis was made and treatment with systemic and intrathecal streptomycin was begun on April 27.

Almost at once he began to improve, and within a few days was virtually free from symptoms. The daily cell counts in the C.S.F. ranged between 830 per c.mm. and 391 per c.mm., and all showed virtually 100% of mononuclears, while no acid-fast bacilli were identified in spite of repeated and prolonged examination of every specimen. We therefore concluded that we had made a mistake in diagnosis and that this was really a case of benign chorio-lymphocytic meningitis. The streptomycin was accordingly withheld on May 3, after one week of treatment.

During the next few days there was little change, except that the patient was perhaps not quite so well in

that he again began to have occasional attacks of headache, vomiting, and diplopia. On May 13 the culture set up from the specimen of C.S.F. obtained on April 26—that is to say, from our original specimen—was found to be positive for *M. tuberculosis*. Treatment was immediately begun again, but, even so, two days later the patient developed a mild right-sided hemiparesis which over the next five days became almost complete. Treatment was continued, and after a long and difficult illness he made a complete recovery except for a residual right hemiparesis and dysphasia.

This was the first of our cases in which this particular syndrome was seen. The short history, the absence of any evidence of systemic tuberculosis, the high cell counts, which were almost 100% lymphocytic, the repeated failure to identify acid-fast bacilli on the films, and, above all, the rapid remission of symptoms during the first week of treatment, led us to substitute a diagnosis of benign chorio-lymphocytic meningitis for our original—and correct—one of tuberculous meningitis. In all probability this mistake cost the patient the full use of his right hand and, had it not been that cultures of the very first specimen of C.S.F. fortunately proved positive, might well have cost him his life.

It is interesting to recall that Trousseau (1867) commented on the marked but transient clinical improvement occasionally seen in cases of tuberculous meningitis and warned the inexperienced not to be deceived by this into adding to the distress of the relatives by changing a bad for a falsely good prognosis. Today the penalty for the same mistake is greater, since it may change a really good prognosis into an unnecessarily bad one.

In these, as in other cases of tuberculous meningitis, the final proof of the diagnosis rests with the bacteriologist. In the case just quoted only single positive cultures were ever obtained, and no organisms were ever identified on examination of the direct films of the lumbar C.S.F. In almost all the other cases acid-fast bacilli were found on films from early specimens of C.S.F. and were often present in quantity. It must, however, be remembered that unless tuberculous meningitis is suspected the appropriate staining and cultural methods may not be used in examination of the C.S.F., when the true nature of the infection will be overlooked.

Changes in the Cerebrospinal Fluid

With one exception the cellular changes in the C.S.F. in these acute cases differed both in quality and degree from those commonly seen in tuberculous meningitis. Accepted limits for the pleocytosis in tuberculous meningitis are 25 to 500 (Merritt and Fremont-Smith, 1937), 10 to 350 (Brain, 1951), and 35 to 300 (Debré and Brissaud, 1953). Other authors confirm these values. All agree that lymphocytes predominate, though as a rule a certain number of polymorphonuclear leucocytes are also present (Smith and Daniel, 1947). The total and differential cell counts before treatment in our cases are shown in Table II. In five cases the C.S.F. at the first lumbar puncture contained over 700 cells per c.mm., and in three there were more than 1,000 cells per c.mm. By the time the first intrathecal injection was given cell counts of 500 per c.mm. or more had been seen in every case but one. Not infrequently these high counts were maintained or even increased during the first days of treatment, but thereafter they usually fell until by the third or fourth week of treatment they were varying within the accepted range (Fig. 1).

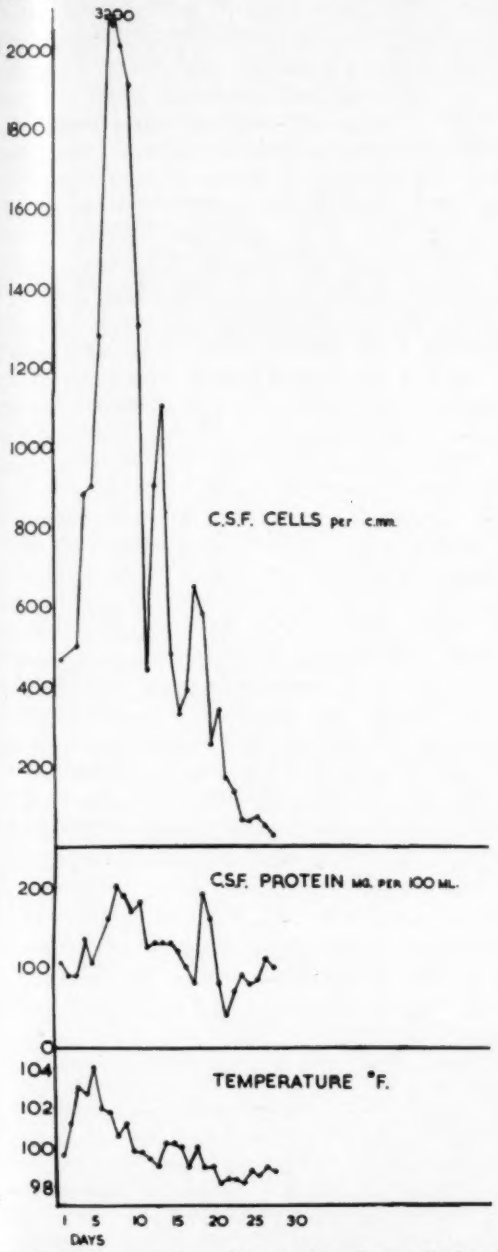
TABLE II

TOTAL AND DIFFERENTIAL CELL COUNTS AND PROTEIN CONTENTS OF C.S.F. BEFORE TREATMENT

Case No.	C.S.F. Cell Counts (per c.mm.) and Protein (mg. /100 ml.)									
	First Lumbar Puncture					Outset of Treatment				
	Total Cells	Polys. (%)	Monos. (%)	Protein	Day of Illness	Total Cells	Polys. (%)	Monos. (%)	Protein	Day of Illness
8	50	0	100	—	7th	674	2	98	450	9th
60	1,600	17	83	840	6th		Same day			
65	514	11	89	210	7th		Same day			
89	740	1	99	180	19th	391	58	42	280	21st
110	469	28	72	105	2nd	500	9	91	90	4th
168	1,070	82	18	50	8th	600*	24	76	120	18th
196	1,300	40	60	320	8th	742	1	99	560	19th
199	891	6	94	200	7th		Same day			
118	88	No differential		200	5th	100	0	100	200	8th

* Burr-holes introduced on the previous day.

FIG. 1.—Graph of the behaviour of cells and protein in the C.S.F. under treatment of Case No. 110 (Smith and Vollum, 1954, Case 1).



In three cases the cells at the time of the first lumbar puncture were virtually all lymphocytes, but in the other four for which full details are known there was a considerable number of polymorphonuclear leucocytes present, and in one case the proportion was as high as 82%. But, with one exception, the number of polymorphonuclear leucocytes rapidly decreased as the illness lengthened, until, by the time that treatment was begun, the pleocytosis was predominantly, if not entirely, lymphocytic. This disappearance of the polymorphonuclear fraction was well seen in Case 196 (Table III), the only case in which serial punctures were done before the institution of chemotherapy.

TABLE III

DETAILS OF C.S.F. FINDINGS IN CASE 196 BEFORE TREATMENT

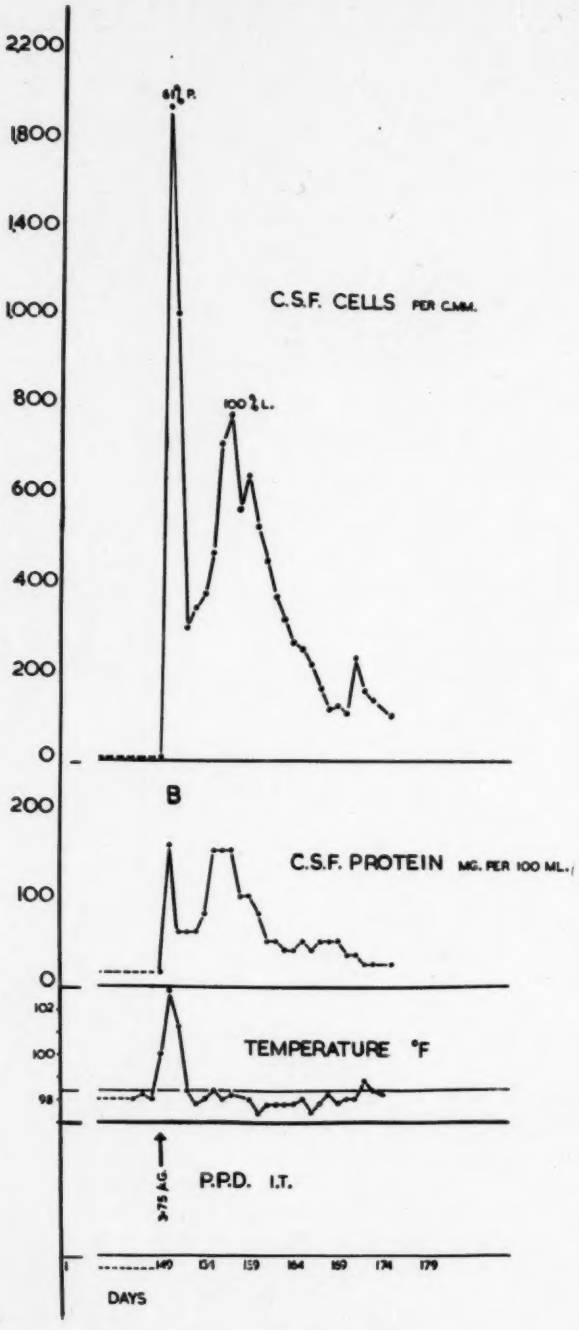
Day of Illness	Total Cells (per c.mm.)	Polymorphs (%)	Protein	Sugar	Chlorides
8th	1,300	40	320	60	760
11th	1,300	10	320	45	720
18th	1,100	10	300	40	730
19th	740	1	560	35	670

The Pathogenesis of the Syndrome of Tuberculous Meningitis of Acute Onset

We have previously presented evidence that the C.S.F. changes of tuberculous meningitis as a whole are the expression of an antibody-antigen reaction : that they are, in fact, the result of an intrathecal tuberculin reaction or series of reactions (Cairns and Smith, 1952 ; Taylor and others, 1954). The close resemblance between the findings in these acute cases and those of the experimental intrathecal tuberculin reaction lends strong support to this hypothesis.

Provided that the recipient is sufficiently sensitive to tuberculin to give a moderate intradermal reaction to 0·1 ml. of old tuberculin 1 in 1,000, 0·75 μg. of the purified protein derivative of tuberculin (P.P.D.) injected intrathecally causes changes in the C.S.F. indistinguishable from the classical findings in tuberculous meningitis (Smith and Vollum, 1950, Fig. 7). When, however, rather larger amounts of P.P.D. (3·75 μg.) are injected the consequent changes in the C.S.F. are greatly accentuated and then mimic very closely those seen in these cases of tuberculous meningitis of acute onset (Fig. 2 : Swithinbank, Smith, and Vollum, 1953, Fig. 1b). This suggests, therefore, that the pathogenesis in these acute cases is the sudden rupture of a comparatively large caseous focus, or " Rich's focus " (Rich and McCordock, 1933), with release of its contents into the C.S.F. These contents will not only be impregnated with tuberculin but will also contain tubercle bacilli which are themselves antigenic. The first result of this rupture will be to flood the C.S.F. with tuberculin-containing material which will then provoke a brisk intrathecal tuberculin reaction. This reaction would be expected to subside in a matter of days, but in the meantime the living *M. tuberculosis* will be seeding themselves in the subarachnoid pathways where, sooner or later, they will

FIG. 2.—The diphasic pleocytosis of the complete intrathecal tuberculin reaction in the normal meninges.



set up a true "caseous tuberculous" meningitis (Lincoln, 1947) with all its established clinical and C.S.F. characteristics.

Both the clinical and C.S.F. pictures in tuberculous meningitis of acute onset can be adequately explained on this hypothesis. The abrupt onset of the signs and symptoms of a mild to moderate meningeal inflammation, without focal neurological signs, is the rule in both the experimental intrathecal tuberculin reaction and of tuberculous meningitis of acute onset. Similarly, the rapid remission of symptoms seen in these acute cases corresponds closely with the cessation of the clinical signs of meningitis seen during the experimental reaction. The only difference is that in the sterile reaction this remission is permanent, while in the natural disease the symptoms of the intrathecal reaction itself are, in the absence of effective treatment, ultimately succeeded by those of an established meningitis.

The correspondence between the C.S.F. findings in tuberculous meningitis of acute onset and those of the fully developed tuberculin reaction is equally precise. During the first 24 hours of the experimental reaction the C.S.F. contains many hundreds, or even thousands, of cells of which the majority are polymorphonuclear leucocytes. In none of our acute cases has the C.S.F. been examined within 24 hours of the onset of symptoms, but, even so, exceptionally high cell counts with, sometimes, a high proportion of polymorphonuclear leucocytes have been seen (Table II). Similarly, when the C.S.F. has been examined a few days after the onset of symptoms the total cell count may still be very high, though the differential count shows that almost all the cells are now lymphocytes (Table III), and this is exactly what is found when the C.S.F. is examined towards the end of the first week of the experimental reaction. The protein content of the C.S.F. is also of the same order in the two conditions.

That a leak of the contents of a tuberculoma can cause a reaction in the C.S.F. indistinguishable from that seen in tuberculous meningitis of acute onset is shown by the following case :

Case No. 74.—This case has also been described by Cairns (1951, Case 1).

A man of 40, who was known to be suffering from bilateral chronic fibro-caseous pulmonary tuberculosis, was admitted to the Radcliffe Infirmary on August 8, 1949, with a three to four weeks' history of morning headache and vomiting. (This case is not, of course, included in our group of cases of acute onset.) Physical examination revealed no abnormal neurological signs whatever. The diagnosis was therefore thought to lie between early tuberculous meningitis and a massive tuberculoma in a silent area of the brain. A cautious lumbar puncture was performed which yielded a fluid under a pressure of 200 mm. C.S.F. containing no cells and 100 mg. of protein per 100 ml. Examination of a direct film of the fluid, however, revealed one acid-fast bacillus. This seemed to confirm the diagnosis of early tuberculous meningitis, and treatment with daily intrathecal and intramuscular injections of streptomycin was accordingly begun. The C.S.F. showed no significant change for five

consecutive days and then, on the sixth day of treatment, the cell count suddenly increased to over 700 cells per c.mm., of which 96% were polymorphonuclear leucocytes. This sudden spike in the cell count subsided almost as rapidly as it arose but was later succeeded by several others, in most of which the cell counts rose to well above 3,000 or even 4,000 cells per c.mm. and of which one, the highest, was accompanied by the sudden appearance of a very large number of tubercle bacilli on the direct film.

Towards the end of the second month of treatment the patient developed a mild right-sided hemiparesis. A little later unmistakable signs appeared of raised intracranial pressure, the patient became decerebrate, and in spite of a sub-temporal decompression he died.

At necropsy no evidence of meningitis was found, other than a minimal milky opacity of the basal meninges. There was, however, a huge tuberculous abscess in the left parietal lobe impinging on a sulcus and filled with liquid pus. When films of this pus were stained by the Ziell-Neelsen method they were scarlet to the naked eye from the enormous numbers of *M. tuberculosis* that were present.

In this case the leaking contents of the tuberculous abscess had provoked a series of intrathecal tuberculin reactions in which the C.S.F. changes bore an unmistakable resemblance to those seen both in the experimental intrathecal tuberculin reaction and in tuberculous meningitis of acute onset.

Confirmatory evidence that the syndrome of tuberculous meningitis of acute onset is the expression of an intrathecal tuberculin reaction is provided by Case No. 118, the only one of our acute cases in which the patient died during the early phase of the illness and where therefore the pathological changes of the presumed spontaneous tuberculin reaction could be studied.

Case No. 118.—A young National Serviceman aged 19 years was admitted from a hospital in Germany to the Military Hospital for Head Injuries late in the evening of February 8, 1951. For the past four months he had been treated with testosterone for an established Fröhlich's syndrome, and during this time had lost 46 lb. in weight. This loss was attributed to the endocrine therapy until February 1, when he began to complain of severe headache and difficulty in finding words. He was admitted to hospital, where he was found to be a little feverish and to be mentally dull and apathetic and to have a mild right hemiparesis with dysphasia. Radiological appearances of the lung fields suggested miliary tuberculosis. Lumbar puncture yielded a fluid under a pressure of 300 mm. C.S.F. and containing 88 leucocytes per c.mm. (nature of cells not recorded) and 200 mg. of protein per 100 ml.

During the next few days there was little change in his condition except that the fever increased, and on the eighth day of his illness he seemed fairly well and was quite alert and able to talk. On this day he was flown home to England, and while in the aeroplane he grew

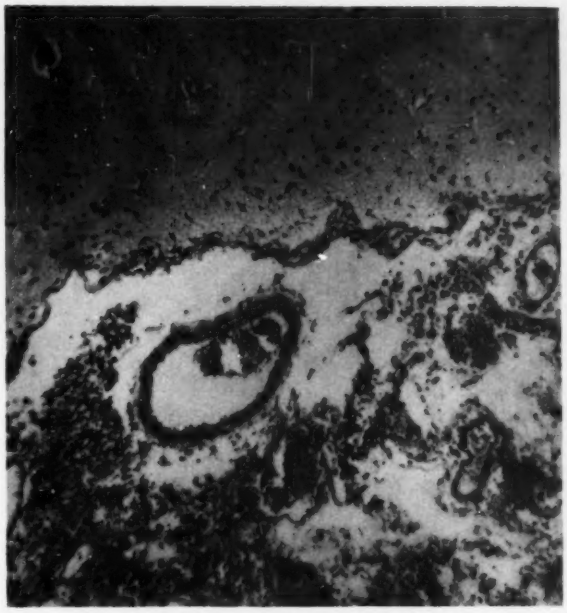


FIG. 3.—Meningeal exudate in Case No. 118.

rapidly worse and by midday was in coma. A lumbar puncture at this time showed that the C.S.F. was again under a pressure of 300 mm. C.S.F., and analysis of the fluid done after arrival at Wheatley showed that it contained 100 lymphocytes per c.mm., 200 mg. protein per 100 ml., while the chloride and sugar contents were 560 mg. and 22 mg. per 100 ml. respectively.

On admission to the Military Hospital for Head Injuries he was profoundly unconscious; the pupils were widely dilated and fixed to light, and the corneal reflexes were absent. The neck was a little stiff, but Kernig's sign was negative. There was no definite papilloedema. The depth of coma made detailed examination impossible, but there was certainly some degree of right hemiparesis. The tone in both lower limbs was increased, and there was a bilateral ankle and patellar clonus. Radiographs of the chest showed the characteristic changes of miliary tuberculosis, and on subsequent retinoscopy choroidal tubercles were identified in each eye.

In the early hours of the next morning the lateral ventricles were tapped through bifrontal burr-holes as an emergency measure. The ventricles were symmetrical and the intraventricular pressure was 200 mm. C.S.F. While the patient was in the theatre a message was received that acid-fast bacilli had been found in the specimen of C.S.F. withdrawn during the flight, and accordingly 100 mg. of streptomycin was instilled into the ventricles. *M. tuberculosis* were later identified in the specimen of ventricular fluid.

Following the ventricular tap the patient at first improved a little, but at 8 o'clock on the morning of February 9 he had an attack of decerebrate rigidity in which his temperature rose rapidly to 105° F., the pulse to 160, and respirations to 54 per minute. The hyperpyrexia was controlled by means of an iced rectal drip,

FIG. 4.—Meningeal exudate in a guinea-pig in the course of an intrathecal tuberculin reaction.

and the patient again improved a little. However, by midday the decerebrate posture was again becoming apparent, and during the rest of the day his general condition steadily deteriorated. He again developed a hyperpyrexia, and just after midnight, at the beginning of the tenth day of his illness, he died.

At necropsy the widespread miliary tuberculosis was confirmed. But to everyone's surprise the naked-eye appearances of the brain were entirely normal; in particular, no tubercles or basal exudate could be seen. When the brain was cut after fixation the absence of any macroscopic abnormalities was confirmed. However, when the stained sections were examined the subarachnoid space was seen to be distended by a profuse generalized cellular exudate (Fig. 3).

According to the hypothesis outlined above, this patient died at the height of a fulminating intrathecal tuberculin reaction. Except for the fatal termination, the clinical events of the last 36 hours of the illness were identical with those twice seen when excessive amounts of P.P.D. were inadvertently given in the treatment of tuberculous meningitis (Smith and Vollum, 1950). Even more conclusive were the post-mortem findings. Not only was the complete absence of any macroscopic changes in the brain in striking contrast to the findings in all our other fatal cases of tuberculous meningitis, but the microscopic appearances were quite remarkably like those seen in experimental animals that had been sensitized to tuberculin and then given an intrathecal injection (Fig. 4) of a large amount of P.P.D. (Bosanquet, Daniel, and Vollum, Fig. 3, 1953).

Discussion and Conclusions

The explanation offered above for the syndrome of tuberculous meningitis of acute onset is thus supported by a considerable body of circumstantial evidence. In the first place, it explains both the abrupt onset and the tendency to spontaneous remission. Moreover, since it has been shown that intrathecal tuberculin is a valuable adjuvant to the chemotherapy of tuberculous meningitis (Smith, 1953), it may help to explain why the prognosis in this group of cases is good, provided that treatment is begun before the patient is moribund. Secondly, it is supported by the marked similarity between the C.S.F. changes in cases of acute onset and those of the experimental intrathecal reaction. Thirdly, it has been shown that a tuberculoma leaking into the C.S.F. is capable of producing changes in the C.S.F. that are strictly comparable with those under discussion. And, finally, the pathological findings when death occurred at the height of the supposed reaction not only differed profoundly from the classical post-mortem findings in tuberculous meningitis, but bore an unmistakable resemblance to those seen in experimental animals killed at the height of an induced tuberculin reaction.

This conclusion, that the syndrome of tuberculous meningitis of acute onset is caused by a particularly well-marked spontaneous tuberculin reaction, supports the hypothesis that the C.S.F. changes in tuberculous meningitis as a whole are a manifestation of a hypersensitivity phenomenon, since it explains so well the anomaly of the unusually high cell count.

The other well-established anomalous finding in some cases of proven tuberculous meningitis of trivial or absent abnormalities in the C.S.F. can also be explained on the same basis. If this hypothesis holds, then a normal, or virtually normal, C.S.F. would be expected either if the patient had for any reason lost the power of reacting to tuberculin (Rich, 1951), or if the meningeal involvement was confined to the depths of a sulcus and did not invade the subarachnoid space as a whole. As it happens,

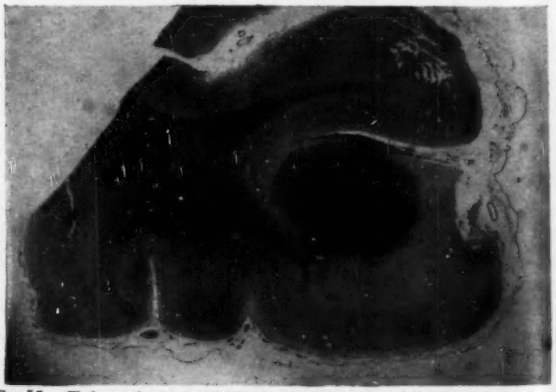


FIG. 5.—Tuberculoma impinging on a sulcus, with overlying exudate. The meninges were normal.

we have seen examples of both these conditions. We have seen a case of overwhelming miliary tuberculosis in which the patient was not only Mantoux negative to 0·1 ml. old tuberculin 1 in 100, but in which both the cell and protein contents of the C.S.F. returned to normal during the first five days in hospital, leaving *M. tuberculosis* present in the C.S.F. as its only abnormality. As the patient improved under the influence of chemotherapy and cortisone, so the Mantoux test became positive and the typical C.S.F. changes reappeared. We have also seen a case of miliary tuberculosis where death occurred in the eighth week of treatment and in which lumbar puncture was regularly performed every week. The C.S.F. was last examined one week before death and was normal in all respects by the strictest standards. Yet at necropsy the brain was found to be studded with small tuberculomata, and though many of these were impinging on the subarachnoid space, and one had actually leaked into a sulcus, the meninges as a whole were perfectly normal (Fig. 5).

We therefore conclude that the C.S.F. changes in tuberculous meningitis as a whole are the expression of an antibody-antigen response, or, more specifically, of a series of intrathecal tuberculin reactions, and that not only the classical C.S.F. findings but both the well established anomalous findings can be explained in this way.

Summary

The syndrome of tuberculous meningitis of acute onset, when complete, consists of an acute or abrupt onset, a tendency to spontaneous remission, unusually high cell counts in the C.S.F., and a good prognosis on adequate treatment.

Evidence is put forward which strongly suggests that the syndrome is caused by a sudden spontaneous intrathecal tuberculin reaction due to rupture of a Rich's focus.

The pathogenesis of the C.S.F. changes in tuberculous meningitis is discussed in relation to these findings.

We are grateful to the War Office for permission to publish some of the cases included in this paper.

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THE PATHOLOGICAL EFFECTS PRODUCED BY SERA OF ANIMALS IMMUNIZED WITH FOREIGN NERVOUS OR SPLENIC TISSUE

PART I: INTRACISTERNAL INJECTION OF SERUM

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There exists one apparent discrepancy between the reports of investigators who, in the opening years of the present century, attempted to produce " neurolytic " or " neurotoxic " sera by immunizing animals with foreign nervous tissue, and those of more recent workers who by rather similar procedures have studied the genesis of the so-called allergic encephalomyelitis.

At a time when the development of various cytolytic sera was a topic of current interest, a few observers (Centanni, 1900; Délezenne, 1900; Pirone, 1904; Armand-Delille, 1906; Schmidt, 1906) injected animals with large doses of foreign nervous tissue, thereby obtaining sera which when introduced intracerebrally into the species providing the nervous tissue caused convulsions, paralyses, and more or less rapid death. On the other hand, a number of experimenters with " allergic encephalitis ", evoked by injections of homologous or heterologous brain-tissue, agree that the sera of affected animals do not reproduce the condition, and apparently do not cause disturbance of any kind when given intraperitoneally, intravenously, or intracisternally (Morgan, 1947; Freund, Stern, and Pisani, 1947; Kabat, Wolf, and Bezer, 1948; Hill, 1949). Moreover, although it has long been known that brain-specific antisera, reacting in the complement-fixation test, can be obtained by immunizing animals with suspensions or alcoholic extracts of foreign brain, the sera in cases of " allergic encephalitis " do not constantly show complement-fixing or other antibodies (see Hurst, 1952).

As mentioned in passing elsewhere (Hurst, 1944), at intervals over the years we have prepared neurotoxic sera in a variety of species; the pathological changes such sera produce under various experimental conditions do not appear ever to have been described in detail.

Experimental

Immunization of Animals.—In an experiment carried out in 1930, a goat received intramuscularly twice-weekly injections of a very thick suspension of simian brain freed as far as possible from blood and connective tissue. There was nothing premeditated in the choice of brain and of animal to be immunized; we merely used what happened to be available. The intramuscular injections were supplemented at irregular intervals by intravenous injections of a centrifuged 10% suspension of brain. Immunization continued for seven months, during which time the goat lost weight but manifested no symptoms of what is now known as " allergic encephalitis". At the end of the period the animal was bled.

Other sera prepared along the same lines between 1930 and 1940 were in rabbits and sheep against porcine brain, and in rabbits against sheep and monkey brain.

Since it appeared desirable to compare the effects produced by the foregoing sera with those of sera resulting from more modern methods of immunization, we have recently twice repeated the initial experiment in two pairs of goats immunized by the technique of Freund and McDermott (1942).

Over a period of two months the animals received intramuscularly seven doses, each of 10 ml., of a water-in-oil emulsion of simian brain with added tubercle bacilli (brain 46 g., phenol-saline 80 ml., paraffin oil 50 ml., dried tubercle bacilli 100 mg., " arlacel A " 20 ml.). In the early stages the goats lost weight, which they regained later in the period of immunization. They were bled 14 days after the last injection, and a month later the lymph nodes draining the parts receiving inoculum were collected.

For purposes of comparison, two other goats were similarly immunized with simian spleen and serum collected at the end of two months.

The control sera used in this work were furnished by the same animals before immunization.

None of the sera was markedly haemolytic in a standard system composed of heat-inactivated serum, guinea-pig complement, and monkey erythrocytes. Thus the recent anti-brain and anti-spleen sera produced

complete haemolysis at 1 in 4, partial haemolysis at 1 in 8 and 1 in 16, and the merest trace at 1 in 32 ; before being lysed the red cells were agglutinated by the sera, and agglutination without haemolysis continued up to a dilution of 1 in 128. In the absence of complement the sera agglutinated simian red cells. If, however, the dilutions of the sera were made with inactivated normal goat serum, and the simian erythrocytes suspended in normal monkey serum instead of in saline, haemolysis was produced up to a dilution of 1 in 128. Normal goat serum was not in itself haemolytic under any of these conditions.

Results

Intracisternal Injection of Neurotoxic Sera.—The following observations are based on the findings in 12 monkeys (*M. mulatta*) given the first preparation of goat serum, six monkeys given the recent samples, eight pigs given immune rabbit or sheep serum, and a number of monkeys and sheep receiving various immune sera. The serum injected was always one prepared against the nervous tissue of the recipient species ; we have performed no experiments to determine whether a serum neurotoxic for one species possesses similar properties for others. No differences were observed in the effects of the samples of goat serum prepared by the two different techniques at an interval of nearly 20 years.

Under ether or nembutal anaesthesia we removed as much cerebrospinal fluid as possible (3 to 5 ml.) and replaced it with a slightly smaller volume of warmed immune serum ; from the results described below, it is evident that under these conditions much of the inoculum found its way into the most remote parts of the ventricular system. Repetition of the procedure became progressively more difficult, and several monkeys died of trauma inflicted upon the medulla in one of the later attempts. The largest number of doses given was five in 18 days. No localizing signs followed the injections, but the animals obviously suffered from meningeal irritation, and their general condition was visibly worse than that of those receiving the corresponding control serum. This was especially the case with goat serum, which in all experiments seemed to be much more neurotoxic than any other of the sera prepared ; it is probably coincidental that the goat is highly resistant to the development of " allergic encephalitis " (Innes, 1951). The serum prepared in rabbits against pig brain was fairly active, while many of the others produced scarcely more severe changes than did the control sera.

Several monkeys apparently fully recovered from the effects of two or three doses of serum, and allowed to remain without further interference, later developed progressive weakness and died with convulsions. At necropsy, as also in several others given multiple doses, the whole ventricular system was greatly dilated, and we were tempted to suppose that the animals had succumbed to the effects of an acute hydrocephalus. Subsequent discovery, in the brains of some of these, of continuing acute inflammatory changes as long as a week after the last dose of serum suggested the possibility of a progressive condition which was not exclusively even though largely mechanical.

Intracisternal Injection of Anti-spleen Serum.—The immediate effects were more severe than those of the anti-brain sera. Doses of 1·5 ml. and more of the undiluted serum killed recipients within four hours ; at necropsy the meninges were greatly congested and often exhibited punctate haemorrhages. By diluting the serum with saline we were able to study the remote effects of single or repeated doses.

Pathological Examination

Microscopical appearances in the brains of animals receiving neurotoxic goat sera were somewhat diverse, and we shall not describe at length a host of pathological minutiae without direct relevance to the main theme of this paper. The diversity was in part related to the number of doses of serum given and the time of necropsy in relation to the last dose, and in part to the fact that no single dose of serum evoked lesions spread uniformly over the whole area potentially exposed to its action. Thus, some areas of the ventricular system of animals receiving multiple doses showed a summation of the effects of several, others the effects of a recent or more remote single dose, while still other areas were apparently unaffected.

In monkeys receiving a single dose of any of the samples of neurotoxic goat serum, and sacrificed within 24 or 48 hours, lesions were found in two situations, in the meninges and in the ventricular system.

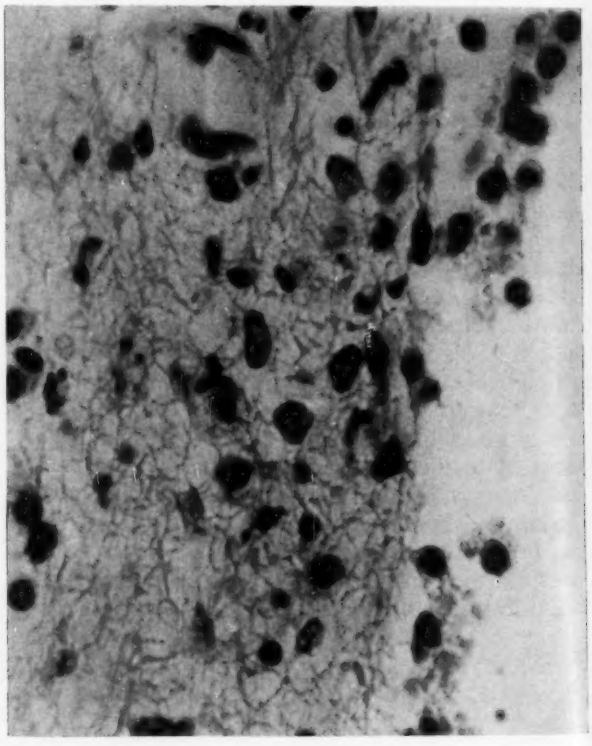
In the former they were usually severe over the cerebellum and brain-stem, the base and lateral surface of the cerebrum, and sometimes on the upper medial surface of the hemisphere. They took the form of a severe and predominantly polymorphonuclear meningitis, with early and light microglial reaction and some polymorphonuclear invasion in the immediately subjacent subpial zone of the most severely affected areas, e.g., the depths of the Sylvian fissure. In other places coagulated fluid (serum) was present and small haemorrhages sometimes occurred. The adventitia of the walls of some main arteries was sparsely infiltrated by leucocytes, but the muscular coat was intact. In some of the veins heavy infiltration continued through the whole thickness of the wall.

FIG. 1.—Perivascular necrosis around a vessel near an affected part of the lateral ventricle. Single dose of neurotoxic goat serum. × 234.

In the ventricular system lesions were seen at all levels up to the lateral ventricles, but nowhere were they continuous over extensive areas. Over large patches the ependymal cells had disappeared, and in occasional foci immediately beneath, or around a nearby vessel (Fig. 1), the cells were degenerating, their nuclei swollen or pyknotic, and the staining of the background altered as in an early infarct or zone of perivascular necrosis. "Ball" or perivascular haemorrhages were sometimes present. In other areas the tissues beneath the denuded surface were infiltrated with polymorphonuclears or showed early mobilization of the microglia (Fig. 2). The choroid plexuses also were involved in a patchy fashion; in places the surface epithelium was lost, in others a small tuft might be necrotic (Fig. 3), while the stroma was widely infiltrated with polymorphonuclears. We may perhaps add that cultures for bacteria were always negative.

Repeated doses of serum accentuated the meningitis (Fig. 4). The earlier waves of polymorphonuclears underwent karyorrhexis and were engulfed by phagocytes; mononuclears including a few plasma cells and some granular corpuscles appeared in animals killed some days after a dose, and swelling and proliferation of the cells of the vascular adventitia and of the mesothelial cells of the meninges added to the picture in many brains. Glial enlargement accompanied microglial reaction in a few areas of the subpial zone. Very rarely a small vessel suffered thrombosis. The ventricular system became considerably dilated, and over much of its extent, but never throughout, was lined by a zone of inflammatory tissue (Fig. 5). The changes were not graded in severity according to distance from the cisterna magna, and on the whole were fully as severe in the walls of the lateral as in the fourth ventricle. Just after a dose of serum the cellular exudate in these areas was predominantly polymorphonuclear, and many cells passed into the lumen of the ventricle. Later, microglial phagocytes containing fine sudanophil granules intermingled with mononuclears and perhaps enlarged glial cells, but in some monkeys massed polymorphs occurred in places as late as seven days after the last dose of serum. Adjacent vessels were infiltrated with polymorphonuclears or mononuclears and their adventitial cells were often swollen and proliferating. Other areas from which the ependyma was absent

FIG. 2.—Desquamation of the ependyma of the lateral ventricle. Oedema, light polymorphonuclear infiltration, and early microglial response in the underlying nervous tissue. Single dose of neurotoxic goat serum. × 750.



showed principally enlarged glial cells, sometimes in the form of a palisade of multinucleated elements (Fig. 6); this appearance commonly obtained in masses of grey matter, e.g., the caudate nuclei, abutting on the ventricles. In one animal patches of the ependyma (possibly regenerated) were several cells deep, and ependyma-like cells were proliferating in rosettes slightly below the surface. In every animal parts of the ventricular surface were apparently normal. Patchy changes in the choroid plexuses have already been outlined; in addition, after several doses of serum, some animals showed in the plexuses large multinucleated giant cells, with or without numerous eosinophils (Fig. 7), and rarely smaller giant cells occurred in parts of the meninges.

Generally speaking, the depth of the cellular zones lining the ventricles was greater in areas of grey matter than where myelinated fibre tracts ran parallel to the surface; this, no doubt, resulted from mechanical factors. The deepest penetration and most severe lesions often occurred at an angle of the ventricles. While in the more severely affected areas the myelin was destroyed together with other constituents of the tissues, no evidence of selective demyelination existed.

Because the appearance of "allergic encephalitis" has been linked with the development of sensitivity of the tuberculin type (Waksman and

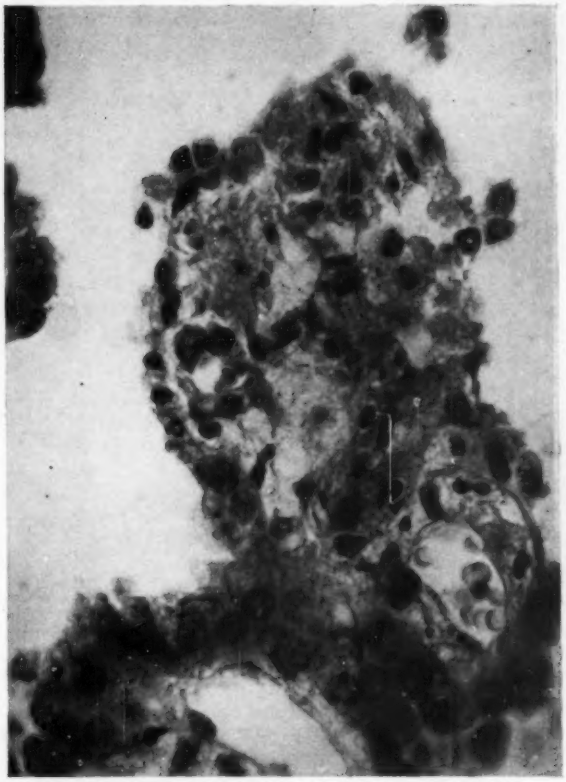


FIG. 3.—Necrosis of a tuft of the choroid plexus in the lateral ventricle. Single dose of neurotoxic goat serum. × 456.

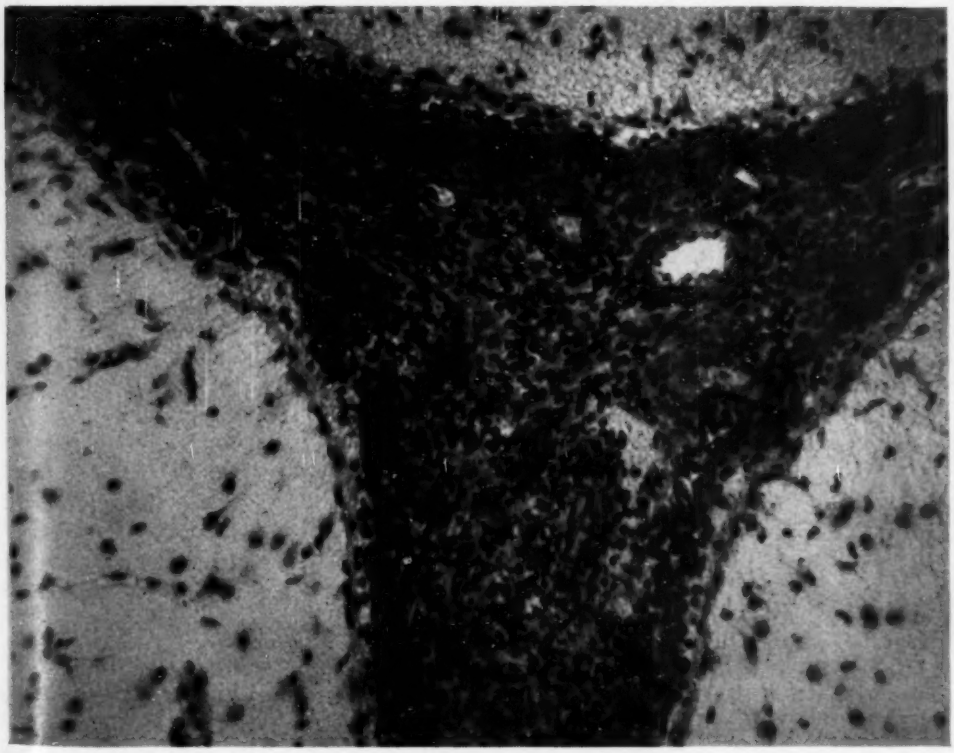


FIG. 4.—Meningitis in the Sylvian fissure. Multiple doses of neurotoxic goat serum. × 234.

FIG. 5.—Zone of inflammatory tissue lining the lateral ventricle. Multiple doses of neurotoxic goat serum. × 140.

FIG. 7.—Large giant cell and inflammatory reaction in a choroid plexus. Multiple doses of neurotoxic goat serum. × 630.

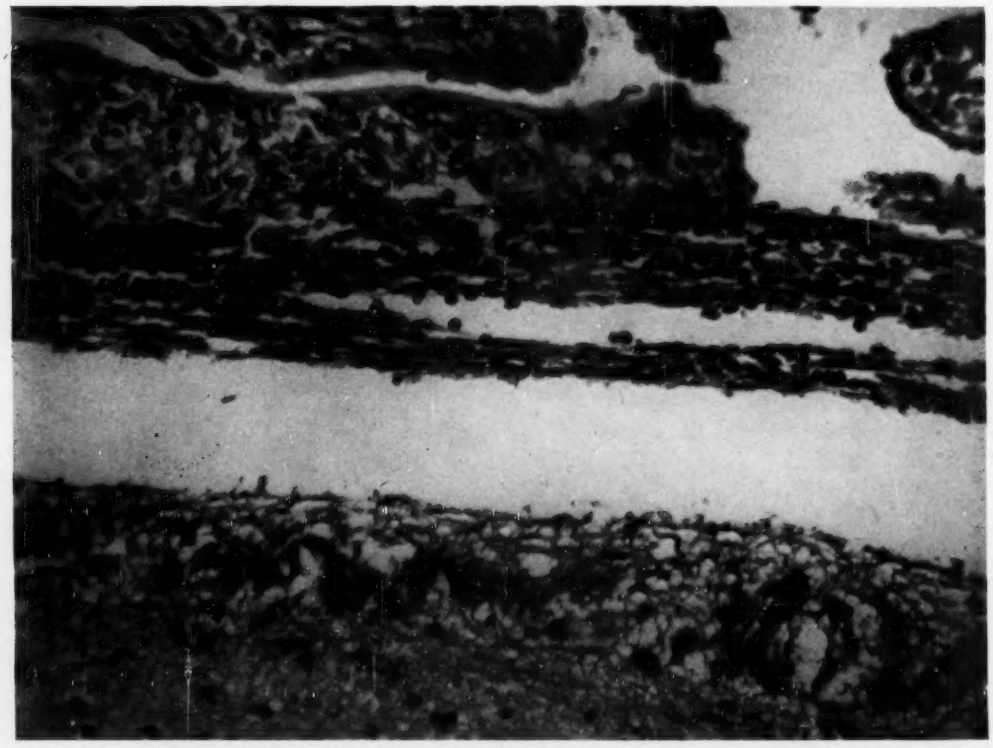


FIG. 6.—Above, inflammation of the choroid plexus : below, palisade of enlarged glial cells beneath a surface denuded of ependyma in the lateral ventricle. Multiple doses of neurotoxic goat serum. × 325.

Morrison, 1951), in the recently immunized goats we removed the lymph nodes draining the areas receiving brain emulsion. A centrifuged 20% suspension of these lymph nodes, given at intervals of three to four days for two and four doses respectively intracisternally in two monkeys, failed to reproduce the condition seen with immune serum and caused only a mild and predominantly mononuclear meningitis.

One of six pigs receiving anti-porcine-brain rabbit serum presented ventricular changes similar to those described above, except that perivascular infiltration occurred at greater depth from the surface of ventricle or meninges. The remainder, together with pigs receiving anti-porcine-brain sheep serum, sheep receiving anti-sheep-brain rabbit serum, and monkeys receiving anti-simian-brain rabbit serum showed meningeal infiltration of varying intensity and nearly always more severe than that produced by the corresponding control serum ; they did not, however, suffer the ventricular lesions. Some of the sera were the outcome of prolonged immunization with the foreign brain material (without adjuvants), and we received the impression that not all animal species are equally suitable as producers of a neurotoxic serum. As far as simian brain is concerned, the goat appears to be a very suitable animal.

Monkeys receiving 1·5 to 3·0 ml. anti-spleen serum and dying within four hours exhibited intense congestion of the meningeal vessels, with many small haemorrhages in places. A massive polymorphonuclear exudate already filled the meshes of the pia-arachnoid over the brain-stem, the cerebellum, the greater part of the lateral surface of the cerebrum, and the upper part of the medial surface ; it continued for short distances, rarely exceeding the depth of the molecular zone of the cortex, along the vessels penetrating the nervous substance. In a few foci polymorphs were numerous also in oedematous areas of the molecular zone, especially along the heavily involved Sylvian fissure. The stroma of the choroid plexus of the fourth ventricle was similarly and densely infiltrated, but upper parts of the ventricular system escaped damage.

With single or repeated doses of anti-spleen serum diluted 1 in 2 or 1 in 4 with saline, lesions were generally similar but milder. The surface of the brains were always more congested than with neurotoxic serum. After three doses of 1 in 2 serum in six days followed by an unsuccessful puncture four days later, a monkey showed a mixed polymorphonuclear and mononuclear meningitis ; where lesions occurred in the superficial zone of the cerebral cortex, the cells were now mainly microglial. In the ventricular system lesions were seen only in the fourth ventricle and were here confined to the stroma of the choroid plexus, leaving the choroidal epithelium, ependyma, and nervous tissues intact. The freedom from change in the upper parts of the ventricular system was no doubt associated with the relatively small inocula—each of 2 ml.—but it appeared also that qualitatively the anti-spleen serum differed from the neurotoxic serum in its negligible effect on the nervous structures proper.

After injection of normal goat serum on one or more occasions, monkeys showed by comparison with the above a very mild and predominantly mononuclear infiltration of the meninges and choroid plexuses. They suffered no loss of the ependyma or of the choroidal epithelium.

Comment

It is clear that the serum of goats immunized with simian brain, whether by long-continued massive injections or more rapidly by modern techniques utilizing adjuvants, acquires the property of exciting very severe nervous lesions when injected intracisternally into monkeys. Neurotoxic sera produced in other species (none, it should be noted, by modern techniques) were less spectacular in their effects, a fact which may perhaps explain in part the failure of other modern investigators to obtain lesions with the sera of animals suffering from " allergic encephalitis ". The lesions we describe differ in several important respects from those produced by a variety of chemical irritants introduced intracisternally (see Hurst, 1955) ; they presumably represent the effects of an antigen-antibody reaction occurring at the sites affected, which are wholly superficial at points in the meninges or on the ventricular surface with which the serum is likely to come in contact. Some of the histological features in animals receiving multiple doses, and in particular the presence of numerous eosinophils and giant cells, are compatible with this assumption. An anti-spleen serum produced in the goat appeared quantitatively more toxic than the anti-brain sera but qualitatively different in attacking only mesodermal structures.

While thus the claims of older writers to have produced sera toxic to the nervous system have been upheld, the present observations make no contribution to the knowledge of how " allergic encephalitis " arises or of whether or how allergy is concerned in the aetiology of the demyelinating diseases of man and animals. Even if a common factor were involved in the production of " allergic encephalitis " on the one hand and of the lesions here described on the other, experiments such as we have

conducted might well fail to bring it to light in view of the highly artificial conditions pertaining to the route of introduction of antibody, concentration at the time of exposure to antigen, and so on. There is, however, no compelling reason to associate the two. The development of " allergic encephalitis " has been linked with the development of sensitivity of the tuberculin type, while many writers witness to the inconstancy and variety of circulating antibodies which may follow immunization of animals with a highly complex system such as nervous tissue. On general grounds it seems more than likely that the lesions we describe are produced by a mechanism different from that responsible in " allergic encephalitis " but further work is needed to substantiate this view.

Summary

Immunization of goats with simian brain resulted in sera with neurotoxic properties. The lesions produced in monkeys receiving these sera intrathecally are described and compared with those following injection of an anti-spleen serum or of normal goat serum. Anti-brain sera produced in rabbits or sheep with the brains of several species were less toxic when introduced intrathecally into the donor species than were those derived from goats.

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SPINO-CORTICAL FIBRES IN MAN

BY

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The purpose of this paper is to present evidence that in man there is a tract which originates in the spinal cord, ascends in the medulla and pons with the cortico-spinal tract, and runs through the internal capsule towards the cerebral cortex. It is also our purpose to draw attention to the older literature on this subject, and to review the evidence presented there.

In 1893 Sottas published a short report entitled "On Retrograde Degeneration of the Pyramidal Tract", in which he described four cases of syphilitic softening of the thoracic region of the cord. In these cases he found degeneration cranial to the lesion in the region of the lateral cortico-spinal tract, which he traced into the cervical cord. In 1894 Gombault and Philippe reported similar findings in four cases. Raymond (1894) also reported a case of syphilitic transverse myelitis; he found, cranial to the lesion in the upper thoracic cord, "considerable diminution of myelinated fibres" and sclerosis in the region of the lateral cortico-spinal tracts; these changes faded cranially, and could not be seen above the third cervical segment; the region of the ventral cortico-spinal tracts was normal. In 1895 Egger found in a case of compression of the cord degeneration in the ventral and lateral cortico-spinal tracts cranial to the lesion; he considered that these were short intersegmental fibres. In 1896 Dejerine and Sottas reported a case of transverse myelitis due to syphilis; they traced degeneration in the region of the lateral and anterior cortico-spinal tracts up into the decussation of the pyramids. In the same year, Dercum and Spiller reported a case of syringomyelia with "ascending (cellulipetal, retrograde)" degeneration involving the lateral and ventral cortico-spinal tract on one side. The most cranial part of the lesion was in the mid-thoracic region. The degeneration could be traced in the lateral cortico-spinal region to the second cervical segment and in the ventral cortico-spinal region to the pyramidal decussation. In 1898 Spiller reported another case. Further cases have been reported by Worotynski (1897), Stewart (1901), Petrén (1903), and Ramsay Hunt (1904). In 1905 Bing reported the case of an infant with anterior poliomyelitis, affecting particularly the upper lumbar segments of the cord. The regions of the anterior and lateral cortico-spinal tracts were full of degeneration granules. From the nature of the pathology Bing had no doubt that these degenerating fibres originated in the grey matter of the cord. He concluded from the position of the degenerating axons that the cells of origin of the ascending fibres within the region of the lateral cortico-spinal tract were situated in the antero-lateral part of the posterior horns and the cells of origin of the ascending fibres within the region of the ventral cortico-spinal tract were in the medial part of the anterior horns. Those in the ventral cortico-spinal tract could be traced cranially throughout the length of the cord; from their position abutting against the median fissure, Bing reckoned them to be part of Marie's faisceau sulco-marginal ascendant. He could not trace the fibres within the lateral cortico-spinal tract above the twelfth thoracic segment. He referred to this case again in his monograph on the spino-cerebellar system (1907), stating that these are ascending endogenous fibres "which can be followed several segments upwards".

From surveying this literature, it is clear that the workers who first described these degenerating fibres never considered that they might be dealing with a true spino-cortical tract. Sottas, Gombault and Philippe, Raymond, Dejerine and Sottas, Dercum and Spiller, Spiller, and Ramsay Hunt, all assumed that this was an example of retrograde degeneration. Gombault and Philippe, however, admitted that it was difficult to distinguish this form of degeneration from Wallerian degeneration. The belief that these fibres are descending fibres showing retrograde degeneration was not held by Egger or by Bing. In that they postulated that these fibres are short intersegmental fibres, they tacitly accepted that they were dealing with true Wallerian and not retrograde degeneration.

The first worker to state that he saw no reason for regarding these fibres as being other than a true

spino-cortical tract, showing Wallerian degeneration, was Choroschko (1909). He reported two cases of compression of the cord in which degeneration could be traced through the pyramidal decussation and the internal capsule into the corona radiata. He gave detailed descriptions of the fibres, but he did not state his staining methods, nor did he give any drawings or photographs. He not only proposed that this was a true spino-cortical tract, analagous to the cortico-spinal tract, but he wrote that there never had been any more reason to consider retrograde degeneration in the case of this tract than in the case of any other divided tracts.

All these earlier observations seem to have been forgotten. Tower (1944) for instance wrote : " All that can be said with certainty is that all fibres running lengthwise in the medullary pyramids are descending fibres ". And Brodal and Walberg (1952): " It was surprising to discover in an experimental cat material prepared for other purposes that there are, in fact, ascending fibres in the pyramid and that such fibres take origin in the spinal cord ". And later in the same paper, they wrote : " It may seem strange that these fibres, as far as we know, have not been observed by previous authors."

Brodal and Walberg's work is particularly important, for they not only showed degeneration in these fibres in the cat by means of the Marchi method, but they also showed it in serial sections stained by Glees' silver method. They were able to follow their ascending fibres into the sixth layer of the cortex : " They could be followed in decreasing numbers to the second layer, the external granular lamina." The area concerned was " the anterior part of the posterior sigmoid gyrus " ; this is the region containing the giant pyramidal (Betz) cells. They observed that the cervical component of this ascending tract " appears to be relatively most important, since there is a pronounced difference between the results of high cervical and those of mid-thoracic lesions ", and they found that " the more caudal the lesion, the more moderate the number of degenerating fibres ".

During the past seven years, while engaged on work on the anatomy of the human spinal cord, we have searched for ascending degeneration in the region of the cortico-spinal tracts. We have come to the conclusion that this degeneration is due to degeneration of a true ascending tract, which takes its origin within the spinal cord and runs, presumably, to cortical cells. This tract follows the path of the descending cortico-spinal tract as far as the cerebral peduncles ; cranial to the pons, in the peduncle, and in the internal capsule the tract lies posterior to the cortico-spinal tract ; here its fibres lie among those of the temporo-pontine tract. The evidence for these statements will now be presented.

Material

Our material comes from patients who had the operation of spino-thalamic cordotomy for the relief of intractable pain. In this operation, fibres of the spino-thalamic, spino-cerebellar, spino-reticular, and spino-tectal tracts are divided. In the majority of these patients, the lesion involved not only these ascending fibres but also some descending fibres lying in, or near, the lateral cortico-spinal tract.

Forty-three patients are considered here ; they are divided into two groups. In the first group are eight patients in whom the operation was performed at the second or third cervical segments. Of this group, three patients died too soon after the operation (six hours, two days, and five days) and one patient too late (313 days) for the application of histological techniques which demonstrate the course of a few degenerating fibres. In the other four patients (Cases 37, 20, 35, and 39) the periods of survival were 81, 110, 112, and 185 days respectively. In the second group are 35 patients in whom the operation was performed at various levels between the fifth cervical and first lumbar segments. In this group the interval between operation and death varied between 12 and 468 days. The evidence for the existence of a spino-cortical tract comes mainly from the first group, and so these cases will be considered in detail ; the cases of the second group provide supporting evidence.

Marchi preparations and/or cell and fibre preparations were made of all levels of the cord and brain, excluding the corona radiata and cortex.

Observations

Case 37 will be taken as an example of the degeneration found in the four cervical cases.

Operation Level (Fig. 1).—The operation was performed at the third cervical segment. The lesion caused by the operation extended dorsally to

All photographs are from Marchi preparations. Degenerating fibres are stained black.

Figs. 1 to 6 are all of Case 37. The interval between the lesion and death was 81 days.

FIG. 1.—Third cervical segment, showing the extent of the lesion caused by operation.

FIG. 2.—First cervical segment, showing degenerating fibres in the cortico-spinal tract cranial to the lesion.

FIG. 3.—Upper limits of pyramidal decussation, showing degenerating fibres in the decussation and in the pyramids, especially on the right, contralateral to the lesion.

FIG. 4.—Pyramids, showing scattered degenerating fibres, more numerous on the right.

FIG. 5.—Cortico-spinal bundles in the pons, with scattered degenerating fibres.

FIG. 6.—The right internal capsule, showing concentration of degenerating fibres in the posterior part.

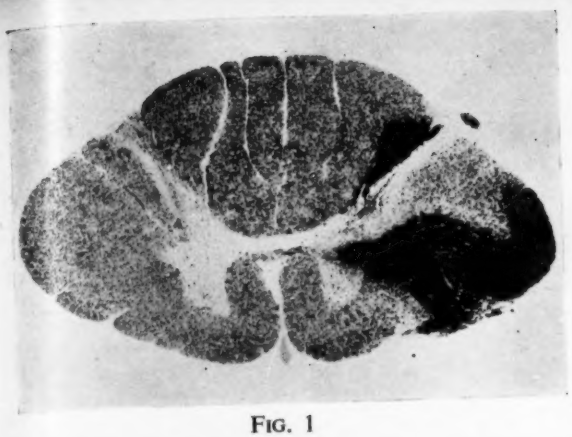

FIG. 1

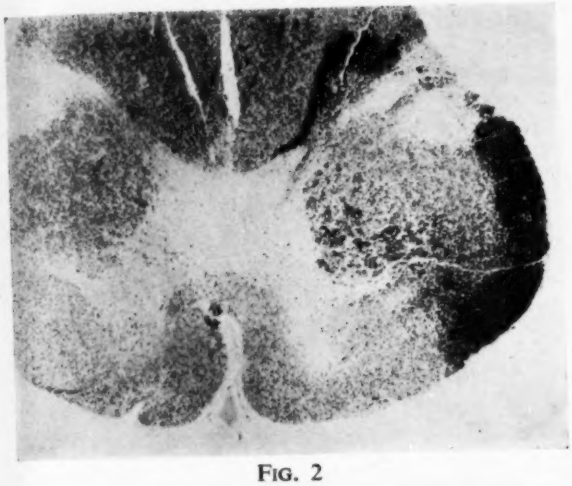

FIG. 2

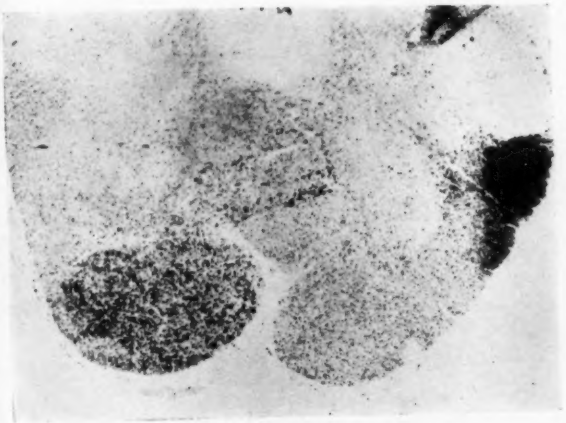

FIG. 3

FIG. 4

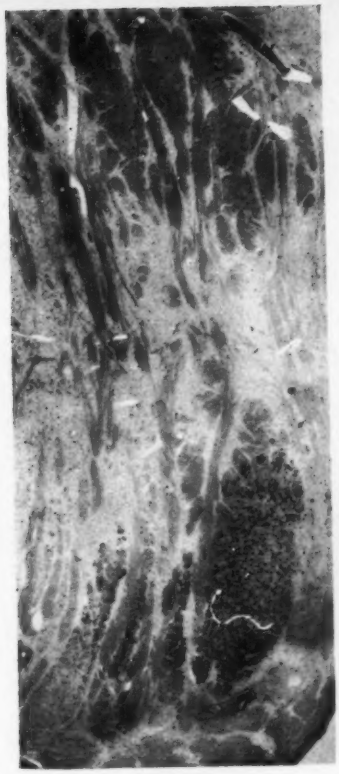

FIG. 5

FIGS. 6a and 6b

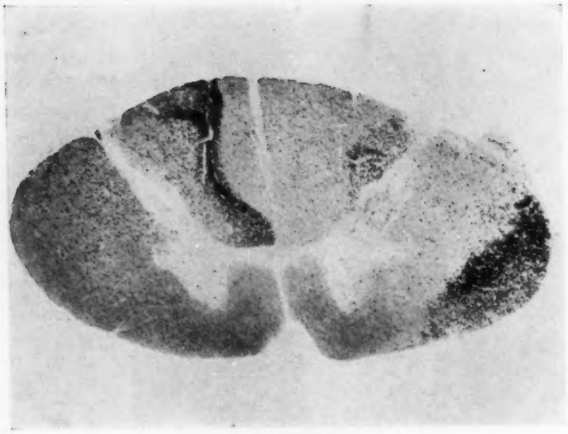

FIG. 7

Figs. 7, 8, and 9 are from Case 35. The interval between the lesion and death was 112 days.

FIG. 7.—Third cervical segment, showing the extent of the lesion caused by the operation on the left, and a small area of softening on the right.

FIG. 8.—Pyramidal decussation showing degenerating fibres from both sides of the cord.

FIG. 9.—Internal capsule at the dorsal limit of the thalamus, showing degenerating fibres in the retro-lenticular part.

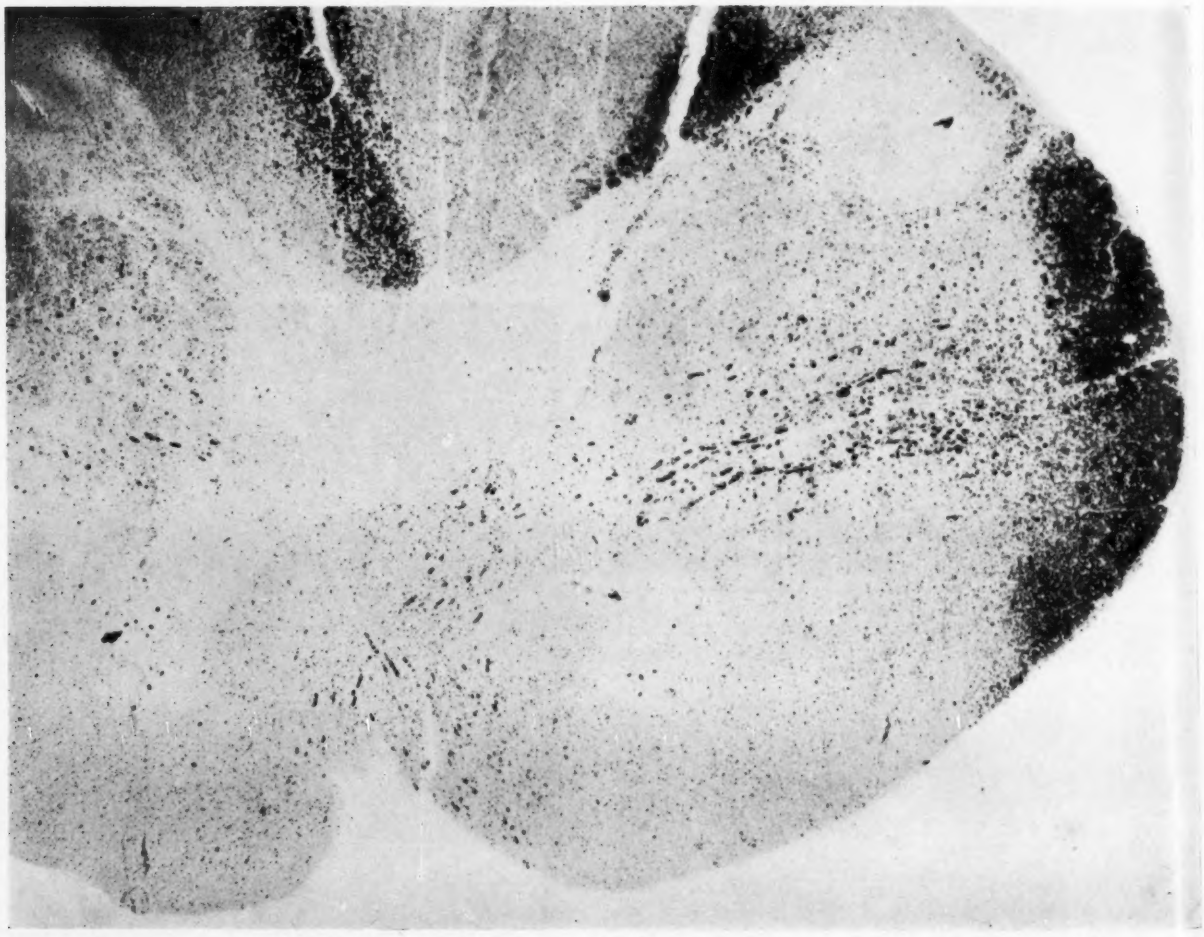

FIG. 8

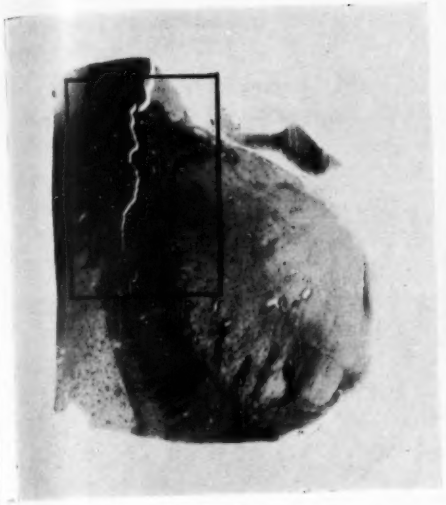

FIG. 9a

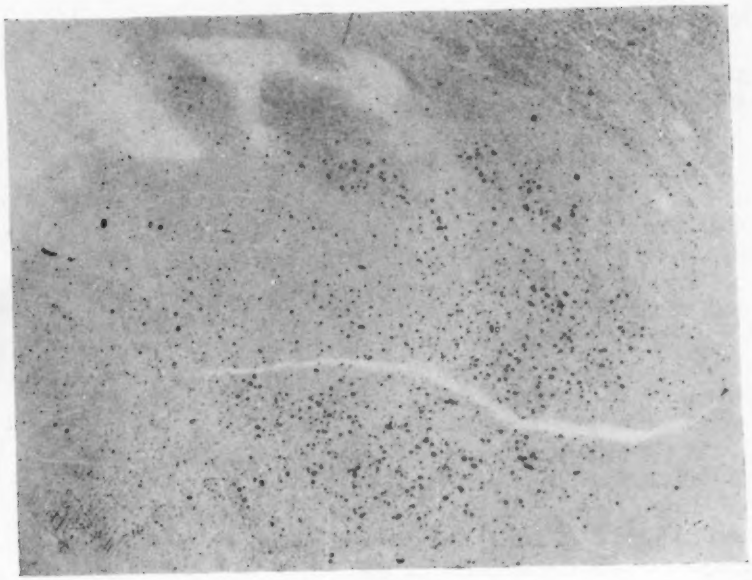

FIG. 9c

FIG. 9b

Figs. 10 and 11 are from Case 39. The interval between the lesion and death was 185 days.

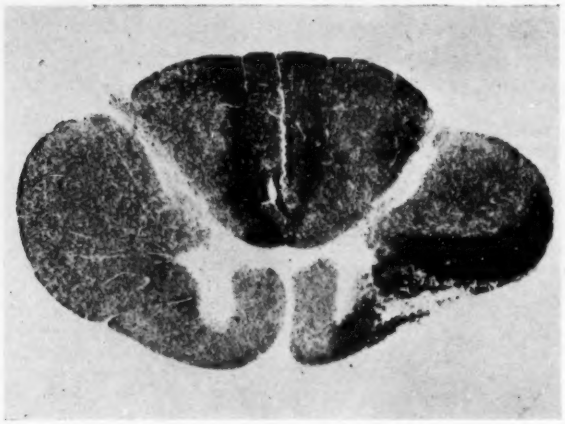

FIG. 10.—Second cervical segment showing the extent of the lesion caused by the operation.

FIG. 11.—Pyramidal decussation showing degenerating fibres passing to the contralateral pyramid.

approximately midway between the denticulate ligament and the posterior horn; it extended ventrally to slightly anterior to the ventro-lateral sulcus, and it extended medially into the grey matter of the cord.

First Cervical Segment (Fig. 2).—Degenerating fibres are present in the ventral part of the lateral cortico-spinal tract. In addition, degeneration is present in the spino-cerebellar, spino-thalamic, and associated tracts.

Upper Level of Pyramidal Decussation (Fig. 3).—Degenerating fibres can be seen crossing in the pyramidal decussation and also scattered throughout the pyramids. The greater number are in the right pyramid, contralateral to the lesion.

Pyramids (Fig. 4).—As in the previous section, the degenerating fibres are scattered diffusely throughout the pyramids, mainly on the right side. There is considerable variation in the size of the Marchi bodies, many being large, comparable to the degenerating fibres of the dorsal spino-cerebellar tract.

Pons (Fig. 5).—The degenerating fibres here, as in the pyramids, are diffusely scattered through the bundles of descending fibres; the majority of them are on the right side. There appear to be fewer degenerating fibres here than in the pyramids.

Internal Capsule (Fig. 6).—Here the degenerating fibres are concentrated in a small area in the posterior part of the internal capsule. This region is that occupied by the temporo-pontine tract. There are definitely fewer degenerating fibres here than in the more caudal sections.

In Case 35 (Figs. 7, 8, and 9) there were two lesions in the spinal cord. In addition to the surgical lesion made on the left side of the cord at the level of the third cervical segment, there was a small area of softening on the right side at the same level, involving the dorso-lateral region (Fig. 7). Degenerating fibres can be traced cranially from both these lesions. In Fig. 8 they are shown in the pyramidal decussation. In Fig. 9 they are shown in a horizontal section of the internal capsule at the level of the dorsal limit of the thalamus. It is to be noted that there is a considerable number of these fibres still present at this level, although the lesion was not extensive and the period of survival was long (112 days). In Case 39 a particularly large number of degenerating fibres is present. The extent of the lesion in the cord is shown in Fig. 10; it will be noted that in this case it was extensive. Numerous degenerating fibres in the pyramidal decussation are shown in Fig. 11. As Case 20 is similar in all respects to Cases 35, 37, and 39, photographs of this case are not shown here.

It is to be stressed that in none of the four cases described here was there any evidence of a lesion of any part of the cortical-spinal system occurring at levels cranial to the operation. As serial sections of the material were studied, even a small lesion would certainly have been detected.

Conclusions from Histological Findings.—In all the cases with lesions in the upper cervical cord, the lesions extended sufficiently far posteriorly to cause clear descending degeneration in, or adjacent to, the lateral cortico-spinal tract. In all these cases there are some ascending degenerating fibres among the intact fibres of the cortico-spinal tract.

It has not been possible to determine the cells of origin of this tract, for the lesion in each case divided the fibres of many ascending systems as well as these fibres. We have mapped out the location of these cells, caudal to the lesion, which show retrograde changes. These cells are in various nuclei of the posterior and anterior horns and of the intermediate grey matter. It is impossible in our cases to determine which of these cells gave origin to the degenerating fibres under discussion.

The course of these spino-cortical fibres is as follows. Most, but not all of them, cross in the pyramidal decussation. They are diffusely scattered in the pyramids and in the cortico-spinal tract area of the pons; further cranially they become concentrated into a small region of the crus and of the posterior part of the internal capsule. In the highest levels of the internal capsule they are confined to the retro-lenticular area. Thus in the capsule their course is not the same as that of the descending cortico-spinal fibres, for they lie posterior to the cortico-spinal tract in the region of the temporo-pontine tract. It seems that many of these ascending fibres must go to the cortex, for there is no other grey matter at this level. It is clear from the fact that there is a gradual diminution in the number of these fibres as they course cranially that not all of them run to the cortex, or even as high as the thalamus, but the end-stations of these shorter fibres have not so far been determined.

It will be remembered that the lesion in our cases was limited to the anterior part of the lateral cortico-spinal tract. It is possible that fibres from the entire cross-sectional area of the lateral cortico-spinal tract do not all go into the retro-lenticular part of the internal capsule.

As has been stated, these fibres were most numerous when the lesion was in the upper cervical cord. Our material does not permit conclusions to be drawn about such fibres arising in the segments

between the third cervical and the first thoracic segment, for in this region we have only two cases, and in both of them the lesion was restricted to the antero-lateral and anterior parts of the cord. We have many cases with more caudal lesions than the first thoracic segment; in these only a few fibres could be traced cranially. From this material it is concluded that the majority of these fibres originate in the cervical region.

If these fibres followed the entire course of the cortico-spinal tract, the question of whether the degeneration which they show is an example of Wallerian degeneration or of retrograde degeneration would be all-important. But as they leave the course of the cortico-spinal tract cranial to the pons they must be a distinctive tract. In view, however, of the reports of the original workers on this subject, it is to be stated that the features of the degeneration in this tract are exactly the same as those of the Wallerian degeneration in all other damaged tracts; in every case, the stage and appearance of the degeneration was identical with that of the spino-thalamic, spino-cerebellar, and cortico-spinal tracts.

The Marchi bodies vary in diameter from 3 to 25 μ, with many in the 15 to 20 μ range. As Marchi bodies represent disrupted myelin sheaths, they cannot be taken as indicating the exact calibre of the fibres from which they came. It would be particularly fallacious to take the smaller bodies as representing only fine fibres for they may represent degenerating myelin from thicker fibres which have broken up. Nevertheless some deductions from the size of the larger Marchi bodies may be made. We have observed that large Marchi bodies occur only in tracts known to contain thick fibres. And so, although we cannot draw conclusions about the fibre spectrum of this tract, we feel justified in concluding that the tract does contain some thick fibres.

It is notable that so many ascending fibres were seen in our material. For the lesions involved the cortico-spinal tract only partially, and the survival periods were so long that much of the terminal parts of the fibres must have completely degenerated and disappeared. Ideal material for working out the detailed anatomy of the ascending fibres within the cortico-spinal tract would be cases in which lesions involved the entire area of the tract and where the survival periods were between five and 40 days.

Conclusions

The facts set out above lead us to the view that the degenerating fibres under discussion represent a true spino-cerebral tract. Supporting evidence comes from the work of Brodal and Walberg (1952). They demonstrated in cats degeneration of fibres arising in the cord and running to the cerebral cortex. The boutons terminaux around the cortical cells show that this is Wallerian degeneration in a spino-cortical tract. Further supporting evidence comes from Brodal and Kaada (1953). They picked up changes in potential difference from the cat's medullary pyramids, following stimulation of cutaneous, muscular, and mixed peripheral nerves in all limbs. Their findings indicated that the ascending fibres at the level of the pyramids are diffusely scattered throughout the area of the cortico-spinal tract. The majority of the ascending fibres appear to be crossed. As, then, there is such a tract in the cat it is reasonable to expect that the fibres we have described do form a spino-cortical tract in man. We therefore interpret our evidence as indicating that this is a true ascending tract, arising mainly in the cervical segments and running to the cerebral cortex. If this work is eventually confirmed by others it will be established that there is a direct pathway from the spinal cord to the cerebral corte capable of conducting impulses at great speed. This would be the only direct pathway known not having any synapses between the cord and the cerebral cortex.

A NOTE ON RETROGRADE DEGENERATION

Forty years after Türck's first description (1851) of the cortico-spinal tract, Sottas (1893), Gombault, and Philippe (1894), and Raymond (1894) described this ascending degeneration within the area of the tract. During these years the idea of a descending cortico-spinal tract had become so firmly fixed that neurologists assumed that degeneration in this area necessarily involved descending cortico-spinal fibres, and therefore must be an example of retrograde degeneration. It came about that the degeneration in the ascending fibres of the lateral cortico-spinal tract area—which Brodal and Walberg (1952) and Brodal and Kaada (1953), and ourselves consider to be a spino-cortical tract—was taken as the typical example of retrograde degeneration. The differences which these earlier workers found in the degeneration of these ascending fibres and that of known descending tracts are due to features of this particular case. For example, the fact that degeneration in the area of the cortico-spinal tract cranial to the lesion was scattered throughout the region of the tract was taken as a main point of differentiation between retrograde degeneration and Wallerian degeneration, for it was claimed that in the latter the entire tract degenerates. However, if these are ascending fibres scattered diffusely among the descending cortico-spinal fibres, it is clear that when only the former

degenerate the picture is bound to be one of scattered degeneration. The concept of retrograde degeneration soon became universally accepted, and yet the basic example of this kind of degeneration is now seen to be based on a wrong interpretation of the evidence.

This subject of retrograde degeneration is so important that we include here this note devoted to it.

Waller (1850) thought that the process of degeneration occurs only in the peripheral separated portion of a nerve. Subsequent workers, however, found changes in the central end of a divided nerve. Klippel and Durante (1895) reported their observations on man and experimental animals and reviewed the subject of degeneration in a series of five papers. They recorded retrograde degeneration (dégénérescence cellulipète) in various tracts and peripheral nerves. They stated that retrograde degeneration can be distinguished from Wallerian degeneration (dégénérescence cellulifugé), as in the former the myelin sheath degenerates, often leaving the axons unaffected, whereas in the latter the axons degenerate before the myelin sheaths. When Gombault and Philippe (1894) described the changes they saw in the ascending fibres of the cortico-spinal tract, they believed, in company with other workers of the time, that retrograde degeneration commonly occurs in the central nervous system in man. They noticed that the picture was very like that of Wallerian degeneration, but, searching for differences, they concluded that in this case some of the fibres showed degeneration of the myelin sheaths without degeneration of the axis cylinders, and that in this kind of degeneration there were no normal fibres immediately cranial to the lesion, although they were to be found in increasing number as the tract was followed cranially.

In the subsequent years many other workers investigated the question of retrograde degeneration ; the majority of them could not find or produce this kind of degeneration. Nevertheless, Ramsay Hunt (1904) wrote of this degeneration in detail as follows :—

> " The retrograde atrophy of the pyramidal tracts at the first glance resembles the usual descending degenerations. On closer scrutiny certain differences become apparent. The sclerosis is less compact, and contains in its meshes innumerable minute medullated nerve fibres, with attenuated myelin sheaths. . . . The axis cylinders are well preserved, although slightly swollen and staining faintly. The retrograde process extends, as a rule, only a few inches above the lesion, and in none of the recorded cases could be followed above the decussation of the pyramids. It is also interesting to note that the pathological changes in the nerve fibres are in a more active stage at the upper limit of the atrophy, i.e., furthest removed from the initial lesion. . . . I can find no record of any case in which the atrophy was apparent before the lapse of two years from the date of the lesion."

In 1906 van Gehuchten reported the results of an experimental study on the rabbit. He found that when the facial or hypoglossal nerve was cut no changes occurred in the fibre central to the cut, but when the nerves were pulled (arrachés) then degeneration indistinguishable from the Wallerian type occurred in the central ends of the fibres. In this case, the degeneration started from the cell body, and was actually an example of Wallerian degeneration, for it was the consequence of the gross changes taking place in the cell body resulting from the tearing of the fibre. Van Gehuchten called this degeneration " dégénérescence Wallerienne indirecte ". He considered that the cells of origin of certain nerves and of certain tracts in the central nervous system died when their axons were cut, and consequently the axons of these cells degenerated from the cell-body cellulifugally. The instances he mentioned of this form of degeneration were the rubro-spinal, the reticulo-spinal, the vestibulo-spinal tracts, and the middle cerebellar peduncle.

All these workers used the Marchi method. No better method has yet been found for showing degenerating myelinated fibres ; but, as is well known, it tends to produce staining artefacts, and, it must be added, with the techniques used by the workers of those times, these were common. Such artefacts cannot always be easily distinguished from the true staining of degenerating myelin sheaths. There is no doubt that this was not fully realized by some of these earlier workers, and that some of their reported examples of degeneration are in fact examples of the artefacts of the Marchi method. It is unfortunate in this context that few of the early workers could illustrate their papers by photographs, which would have made possible a reassessment of the significance of their findings in the light of later knowledge.

Cajal (1928) in his detailed studies of degeneration processes shows fibres degenerating back to the nearest collateral. He wrote : " The maintenance of the connexion, and therefore the continued functioning, of a collateral, constitutes a hindrance to traumatic degeneration."

Lance (1954) studied retrograde degeneration in the cortico-spinal axons of the cat, following lesions made in the medulla. He came to the conclusion that " an injured pyramidal axon degenerates back to the last node of Ranvier " within some weeks of the injury, and that in the subsequent months it degenerates back to the last collateral. He added

that " the possibility that some descending pyramidal fibres undergo complete retrograde degeneration back to the cortex cannot be excluded ". But as he did not examine material cranial to the pons, evidence for the actual occurrence of such degeneration was not available.

In considering the work on direct retrograde degeneration, it seems to us that two different forms of this degeneration have been described. There is degeneration throughout the length of a fibre, total degeneration, and there is degeneration present for only a few millimetres central to a lesion, local degeneration. In our opinion, satisfactory reports of the local form of retrograde degeneration have been given, but we have found no reports of total degeneration giving adequate distinctive features which justify one in believing that this total retrograde degeneration differs from true Wallerian degeneration. We therefore doubt whether its existence has been proved.

With regard to the total indirect Wallerian degeneration described by van Gehuchten, the changes spread from the cell-bodies peripherally and not from the periphery centrally, as they do in Wallerian degeneration. Thus, if the entire tract were examined the majority of degenerating fibres would be found near the cells of origin—the contrary to what is seen in true Wallerian degeneration or in direct retrograde degeneration.

As this whole question of retrograde degeneration became important in our studies of tract degenerations, we examined in detail many hundreds of sections from our series of 43 cases. These cases are particularly suitable for investigations of degeneration, as the length of time between the lesion and death is accurately known, the lesion in the cord being a surgical one. We also examined sections of spinal cords from many patients who had at the time of death heart failure, uraemia, alcoholism, cancer, pulmonary tuberculosis, and Parkinsonism.

From this material we conclude that retrograde degeneration occurs in the local form but not in the total form affecting an entire tract. Although we have occasionally seen a few fibres degenerating for a few centimetres in a direction which could be considered as cellulipetal, we cannot accept such changes as adequate evidence of retrograde degeneration. The reasons for this are as follows. First, we have never been able to trace such degeneration back to the cell body, even when the relevant cell bodies have shown gross changes, amounting sometimes to loss of many cells in some nuclei. Secondly, in the spinal cord tracts overlap and intermingle ; in any tract there may be a few fibres belonging to another system running in the reverse direction from the main mass of fibres. Thirdly, in view of the nature of the Marchi method, the presence of only a few black bodies central to a lesion needs to be interpreted with great caution. Only when such bodies occur constantly in a certain distribution would we be ready to regard them as significant. Considering these facts, we have never seen any evidence of total retrograde degeneration throughout the length of a tract.

Summary

Ascending fibres within the region of the cortico-spinal tract are described in man.

These fibres, intermingled with those of the cortico-spinal tract, run through the pyramidal decussation into the pons. In the cerebral peduncle and internal capsule they lie posterior to the cortico-spinal tract in the region occupied by the temporo-pontine fibres.

In this material most of these fibres were found to be arising in the upper cervical segments of the cord.

It is concluded that these fibres form a spino-cortical tract.

The subject of retrograde degeneration, which is relevant to the degeneration in this tract, is discussed, and some observations on its non-occurrence are reported.

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ON THE MUSCULAR RIGIDITY AND HYPERREFLEXIA DUE TO HYPOTHERMIA IN MAN WITH OBSERVATIONS ON THE ACCOMMODATION OF PERIPHERAL NERVE

BY

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Before the development of controlled hypothermia as a therapeutic measure in man little was known of the effects of prolonged lowering of the body temperature in the human subject. The pioneering work of Smith and Fay (1940) and of Talbott (1941, 1944) in the use of refrigeration for the treatment of malignant disease, schizophrenia, and intractable pain has found little support and the technique is now most widely used as a means of lowering metabolism during surgical operations (Lewis and Taufic, 1953). The earlier work enabled studies to be made on the conscious subject in conditions suitable for observation. The effect of progressive hypothermia on the human nervous system was described by Davis (1940), Fay and Smith (1941), and Dill and Forbes (1941). A striking feature of these reports was the hyperreflexia and muscular rigidity shown by the majority of patients at a particular range of temperatures. These authors were unable to give a satisfactory explanation of this phenomenon. This paper reports observations on a case of spontaneous hypothermia which suggest a possible mechanism.

The clinical picture of progressive hypothermia is described by Fay and Smith (1941) in a report based on a study of 42 patients who were treated by controlled cooling for various malignant diseases. In three patients, in whom spinal anaesthesia was used during the early stage of refrigeration, cerebration was progressively delayed with the reduction of body temperature. Mental faculties were fairly well preserved until the body temperature approached 93° F. but there was retrograde amnesia for the period during which the body temperature remained below 92° F. Dysarthria began at approximately 93° F. and response to the spoken word became practically nil below 80° F. Pain present before refrigeration was completely relieved in all but 4·7% of the 42 cases but appreciation of pain, heat, and cold was not lost during or after refrigeration as long as consciousness was retained. The pupils remained equal, regular, and normal in size throughout the hypothermic period, but response to light stimuli became progressively more sluggish as the body temperature was lowered. The light reflex was abolished at 78° F. The psychical and pupillary changes resemble those of pharmacological anaesthesia and, indeed, it would not be surprising that the cerebrum should cease to function when its metabolism is lowered by cold (Fazekas and Himwich, 1939) in a manner closely resembling the effects of chemical inhibitors of metabolism. An unusual feature, however, compared with chemical anaesthesia is the retention of muscle tone and the stretch reflexes. The clinical picture vividly described by Fay and Smith (1941) emphasizes this unique feature :—

> " As the body temperature was lowered, the muscles of the extremities assumed a waxy stiffness and when percussed contracted slowly, with subsequent slow relaxation and return to their normal contour. Spontaneous myokymia was observed in patients with temperatures as low as 84° F. ; if the phenomenon was not present at this temperature level, it occurred when passive motion of a joint was made.
>
> The patients assumed a characteristic posture denoting cold, with arms held close to the sides and hands against the upper portion of the chest and beneath the chin.
>
> The upper and lower extremities assumed a flexed position, and considerable effort was required to extend them. In a strong patient it was frequently difficult to extend the arm sufficiently to take blood pressure readings. The wrists were flexed ; the hands did not form the fist position but took a 'clawlike' attitude. The metacarpo-phalangeal joints remained extended, though the interphalangeal joints remained flexed. The patients attempted to curl up into a ball during the shivering phase. When the rectal temperature was reduced below approximately 85° F. shivering ceased and the patients were comparatively comfortable though not relaxed, for the increased muscular tone remained. . . . All volitional movements became progressively slower and incoordination gradually more pronounced as the body temperature continued to fall. The slowed hypertonic movements of the Parkinsonian state are simulated, though the incoordination noted here was more pronounced. No athetotic, dystonic, or choreic movements were observed.

. . . The deep tendon reflexes, abdominal, and gag reflexes were abolished at a temperature level approximately 78° F."

No extensor plantar reflexes were seen in subjects who did not show this response before cooling. There were no permanent neurological sequelae on rewarming. It is not clear from their account whether the characteristic posture and muscle stiffness persisted after the deep reflexes had disappeared but Dill and Forbes (1941), describing similar cases, mention that rigidity and hyperreflexia may be present when the body temperature is only slightly reduced and absent at lower temperatures. Davis (1940) thought that the " pseudospasticity " was probably local though his cases also showed hyperreflexia. Gagge and Herrington (1947) state that resuscitation is unsuccessful if refrigeration is taken to the stage at which rigidity ceases.

Severe muscular rigidity was observed in a case of accidental hypothermia reported by Laufman (1951). He seems to have considered that the muscles were actually " frozen ", though the point is not discussed. Increased reflex activity and resistance to passive movement were prominent in the subject of the present report.

Case History

A 77-year-old man was found by the rent collector lying apparently dead in the house in which he lived alone. He had not been seen by his neighbours for four days. The police were called and it was then established that, although the body was extremely cold, the man was breathing. He was admitted to the Western Infirmary, Glasgow, on February 17, 1953.

The general state of nutrition was fair but the tongue was dry and the eyeballs soft. He had a two or three days' growth of beard ; the body hair was normal. There was a bruise on the right shoulder and a purpuric rash on the front of the thighs. The face and limbs were cyanosed. A clinical thermometer in the mouth did not record. A lotion thermometer inserted about 2 in. into the rectum recorded 22·5° C. (72·5° F.). Respiration was infrequent (7/min.) and shallow. No pulses could be felt in the limb or carotid arteries ; the heart sounds were inaudible. The peripheral veins, however, were full and refilled rapidly when emptied.

On admission he was deeply comatose and did not respond to painful stimuli but during further examination he became restless and made powerful movements of all four limbs. Resistance to passive movement of the limbs was considered normal or slightly increased and was maintained throughout the range of movement. There was no nuchal rigidity and Kernig's sign was absent. All tendon reflexes were present and symmetrical. The abdominal reflexes were absent ; the plantar responses were flexor. The pupils were contracted and did not react to light. The eyeballs were fixed in the mid-position. The corneal reflexes were absent. The fundi could not be seen because of corneal abrasions.

No primary cause for the profound hypothermia was evident. Urine, obtained by catheterization, contained no abnormal constituents.

Progress.—The body was warmed slowly by a radiant heat cage. Frequent measurements of temperature were made with a rectal thermometer and a thermocouple skin thermometer on the forehead (the only accessible area clear of the heat cage). After two hours of warming, the rectal temperature had risen to 23° C. and the radial pulse became palpable. The respiratory rate rose to 12 per minute. Restlessness increased and movements of the limbs became more powerful and hard to restrain ; passive extension of the arms was particularly difficult, causing difficulty in using a sphygmomanometer. For a period between four and eight hours after admission a systolic pressure of 50 to 60 mm. Hg was recorded. An E.C.G. at three and a half hours (rectal temperature 25·5° C.) showed sinus rhythm at 32 per minute with a prolonged Q-T interval and shallow inverted T waves in the three standard leads.

Haematological examination (Dr. H. Conway) showed severe thrombocytopenia, absolute lymphopenia, total absence of eosinophils, and a " shift to the left " of the neutrophil series.

Biochemical findings were : plasma urea, 143 mg.% ; plasma non-protein nitrogen, 108 mg.% ; plasma proteins, 6·36 g.% (albumin 4·33, globulin 1·74, fibrinogen 0·29) ; plasma chlorides (as NaCl), 570 mg.% ; serum calcium, 9·5 mg.% ; serum inorganic PO_4, 6·8 mg.% ; blood sugar, 90 mg.% ; plasma cholesterol, 152 mg.%. The cephalin flocculation test was negative as also that for colloidal gold.

The rectal temperature rose slowly (about 1° C. per hour) during the first 10 hours after admission and the patient's general condition seemed better. Though he did not recover consciousness he continued to resist passive movement and began to withdraw from painful stimuli. When not disturbed he lay on his back with his elbows close to his sides, arms flexed, fingers clenched, and knees drawn up. At intervals he made strong extension movements of a single limb. The tendon jerks were then very brisk. After 10 hours the pulse again became difficult to feel and the rectal temperature stopped rising. Roving dissociated movements of the eyeballs were noted. An intravenous drip was started and over the next seven hours two pints of plasma and one pint of 5% glucose were given. The radial pulse returned but the blood pressure was still not recordable. An E.C.G. at 17 hours (rectal temperature 31° C.) still showed sinus bradycardia with occasional auricular extrasystoles but the Q-T interval was shorter and T_1 and T_2 were now upright. From 18 to 22 hours his condition remained stationary and thereafter slowly deteriorated. He died 23 hours after admission.

Nerve Accommodation.—By the method of Solandt (1936) and with Andrew's (1952) stimulator three measurements of the time-constant (λ) of accommodation (Hill, 1936) of the right ulnar nerve were made when the rectal temperature was 23 to 26° C. The values of λ calculated from the curves shown in Fig. 1 were in the range 128 to 235 m.sec. The range in 32 normal adults

was 30 to 100 m.sec., which agrees closely with the findings of Kugelberg (1944). The values obtained in the hypothermic patient are comparable with those found in patients with latent tetany (Fig. 1).

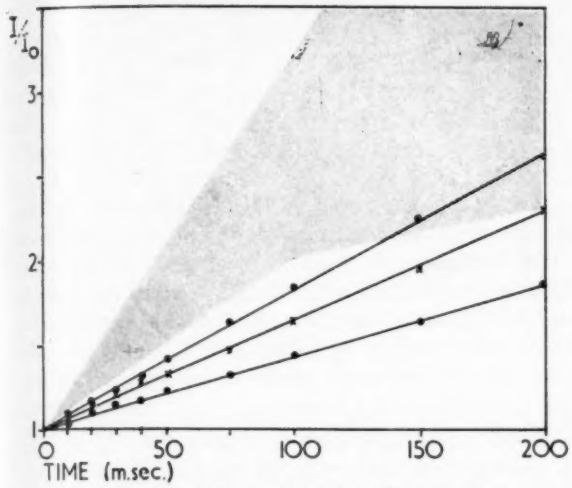

FIG. 1.—Three curves of threshold of the right ulnar nerve at the elbow to progressively rising (exponential) currents. Ordinate in multiples of rheobase (R = 1), abscissa in m.sec. (time-constant of current rise). The index of response was a palpable twitch of the flexor carpi ulnaris at the wrist. The time-constant of accommodation (λ) is the reciprocal of the initial slope of the curve. (The shaded area shows the range of the accommodation curve of the ulnar nerve at the elbow in normal adults.)

Post-Mortem Examination.—Necropsy performed by Dr. H. E. Hutchison 18 hours after death showed aleukaemic lymphatic leukaemia with terminal hypostatic pneumonia. There were two small areas of cerebral softening, one in the right insula (1 cm. diameter) and an even smaller one in the right upper medulla. The brain, spinal cord, and peripheral nerves showed no other macro- or microscopic lesion. The glycogen content of the liver was severely reduced and none was present in a sample of the thigh muscle. The pituitary body was normal and the thyroid (7 g.) and adrenals (total 8 g.) though small were microscopically normal. In particular, the lipoid content of the adrenal cortex was not reduced.

Cause of Hypothermia and Death.—Because of the absence of hypothalamic, bilateral medullary, cervical cord, or endocrine disease sufficient to cause hypothermia from disturbance of thermoregulation and since there was evidence suggesting a fairly heavy fall on the right side, it is presumed that this old man fell, probably with sufficient severity to cause concussion. The small cerebral infarcts seemed too recent and too small to have caused his collapse. Bender (1928) and Rewerts (1949) found congestion and miliary haemorrhages in all parts of the brain in men who had died after prolonged exposure to severe cold. There was also vacuolization of nerve cells in Bender's (1928) case. In the present case the cause of hypothermia is uncertain. The aleukaemic leukaemia must surely have been coincidental. It seems likely that, after a fall, the patient lay, probably unconscious, for three or four days. He was indoors and well clad and the weather was average for the season. The maximum and minimum temperatures in Glasgow during the four days were 48° F. (9° C.) and 30° F. (−1° C.) respectively. These temperatures were higher than those to which other reported patients with accidental hypothermia were exposed but, bearing in mind the age of the patient and the period for which he lay immobile, the climatic conditions were sufficient to cause hypothermia when it is considered that an unclothed conscious person remaining as motionless as possible while tensing all the limb muscles is unable to prevent a slow fall in body temperature at an environmental temperature as high as 27° C. and finds this very exhausting work (Hardy, Milhorat, and DuBois, 1938). It has been calculated (Hardy and Soderstrom, 1938) that an ordinary sized man, exposed nude at 23° C., would have to produce at least 2,300 to 2,500 calories per day simply to maintain body heat and that below 28° C. the motionless human body cools as a physical body. The exhaustion of liver and muscle glycogen, with evidence of adequate thyroid, pituitary and adrenal function, suggests that the normal heat conservation mechanisms had been fully utilized and exhausted.

Discussion

The lowest rectal temperature compatible with life is unknown. In the human subjects of German experiments, sudden cooling of the body in water at 4 to 6° C. invariably caused death when the rectal temperature fell below 28° C. (Gagge and Herrington, 1947), but survival with a lower rectal temperature resulting from gradual exposure to cold air has been recorded (Reincke, 1875; Laufman, 1951). Laufman's (1951) case is the only one recorded in which the rectal temperature was lower than in the present patient.

The circumstances of accidental hypothermia and the overruling requirements of therapy restrict the amount of physiological observation possible but there is a unique advantage in that observations can be made on patients with a body temperature lower than would be justifiable in therapeutic or experimental hypothermia. The patient reported here showed profound suppression of all vital activity and, indeed, was barely living. The post-mortem findings suggest that his body's metabolism was insufficient to counter its loss of heat to the environment. When the body was heated slowly the pulse rate gradually increased, respiration deepened, and the patient began to make reflex responses to cutaneous stimuli. The eyeballs, at first fixed, began to rove independently. The tendon reflexes were never completely absent and were brisk even when the rectal temperature was 22·5° C. The resistance of the limbs to passive movement was considered normal. As the temperature increased, the response to sensory stimuli became more generalized and

even violent. At this stage (rectal temperature 26° C.) the arms were held close to the side with the forearms flexed and the hands clenched ; the thighs and legs were flexed. The position recalls that described by Fay and Smith (1941). The tendon jerks were then very brisk but the plantar reflexes remained plantiflexor throughout. The resistance to passive movement was then greatly increased ; it became extremely difficult to extend the arm for recording the blood pressure. When the observations were made it was considered that the increased resistance to passive movement was due to uninhibited withdrawal from stimuli and that the posture was similar to that adopted by other unconscious subjects, but the subsequent review of the literature on hypothermia suggests that this is not an adequate explanation since one has to postulate a state of increased reflex activity accompanying a profound cerebral inhibition but without obvious pyramidal or extrapyramidal damage in life or on post-mortem examination. It seems probable that the remarkable retention of muscle tone and reflex activity was of the same order as that described by Fay and Smith (1941). These authors recorded the phenomenon without explaining it. Dill and Forbes (1941) were equally at a loss while recognizing that the muscles could hardly be in a state of voluntary contraction, nor could the condition be described as a true " cold rigor " of muscle since it was abolished by further lowering of the temperature. Contracture, abolished by further cooling but reappearing during rewarming to a certain temperature range and leaving no sequelae, could not be due to the necrotic lesions described in frozen muscle by Nageotte (1937) and by Smith, Ritchie, and Dawson (1915), and in immersion foot by Blackwood (1944), nor would a myogenic contracture be accompanied by hyperreflexia. Kottke, Phalen, and Visscher (1944) considered the possibility that the muscular rigidity was due to " non-apparent shivering", which would give the phenomenon some survival value. Certainly dogs subjected to cold show muscle rigidity at a temperature below that at which shivering disappears (Hegnauer and Penrod, 1950). Similar phenomena were noted during cold narcosis in cats by Simpson and Herring (1905) and Hamilton (1937). It is possible that cold affects both the excitation and the contraction mechanisms of skeletal muscle by slowing metabolic processes (Walker, 1949).

In laboratory animals cold has been shown to enhance spinal reflex activity (Toennies, 1938 ; Grundfest, 1941), to cause synaptic facilitation (Granit and Skoglund, 1945), and to induce iterative response of peripheral nerve (Katz, 1936 ; Hoff and Grant, 1944). The latter phenomena are attributed to reduced nerve accommodation (Schoepfle and Erlanger, 1941 ; Erlanger, Blair, and Schoepfle, 1941 ; Skoglund and Uvnäs, 1943). The time-constant of accommodation of frog nerve was shown to be increased by cooling by Solandt (1936) and by Schriever and Cebulla (1938). No complementary studies have been reported in the human subject. In the patient reported above the time-constant of accommodation of the right ulnar nerve was 128 to 235 m.sec. which is comparable with that found in latent tetany. No hypocalcaemia was present in this or in other recorded cases (Bernhard, 1940 ; Talbott, 1941). These workers found no evidence of alkalosis ; indeed hypothermic patients tend to develop acidosis (Dill and Forbes, 1941). The other cations were not determined in this case but the plasma sodium and potassium levels have been normal in the cases in the literature except in the presence of renal azotaemia (Laufman, 1951).

Diminished accommodation of peripheral nerve (increased λ) is usually accompanied by lowering of the rheobase (Kugelberg, 1944) and results in repetitive firing of motor-units in response to a single stimulus to the axone or arising spontaneously as in manifest tetany. It seems highly probable that this is a major factor in the hyperreflexia of hypothermia and the hypertonic state may be analogous to spontaneous tetany. If a peripheral nerve is further cooled, increased refractory period (Adrian, 1914) and conduction block (Gasser, 1931) become dominant until eventually " cold block " occurs. The biphasic effect suggested here is not peculiar to cold. Almost identical results follow various grades of ischaemia in a peripheral nerve. It seems probable that cold and anoxia each slow and eventually prevent enzymatic processes responsible for the oxidative metabolism of nerve which maintains membrane potential and restores the membrane after depolarization (Lorente de Nó, 1947). Unfortunately I was not familiar with the physiological literature when the observations were made and the accommodation curves were not computed immediately so that the resemblance of the muscular rigidity to that of tetany was not appreciated.

It is possible that cold may have a similar action on the accommodation of muscle fibre, and indeed this is the probable explanation for the well-known potentiation of myotonia by cold, but such an action could not explain the muscular rigidity observed unless accommodation was so reduced as to cause prolonged spontaneous firing of muscle fibres. The technique of investigation used is a measure of nerve excitability and does not give information about the state of the muscle. I have investigated

the accommodation of nerve and muscle in myotonia congenita and dystrophica. In these conditions the muscle accommodation is lowered but the accommodation of peripheral nerve is normal. The so-called " myotonia " of hypothyroidism is due to slow relaxation of the contractile substance and not to repetitive firing of muscle fibres. This type of hypometabolic activity may well be present in hypothermia (Walker, 1949) but obviously cannot explain the maintained rigidity.

It is not suggested that shivering has a similar mechanism since it has been shown to be dependent on central pathways (Uprus, Gaylor, and Carmichael, 1935), though a change in peripheral nerve accommodation might serve as an economical amplifying factor. Burton and Bronk (1937) have noted a change in the quality of spontaneous muscle activity (of cats) as cooling increased.

Later observers may be able to answer two questions : (1) Is cold rigidity present in the lower limbs of a paraplegic patient, and (2), Can the Trousseau phenomenon be demonstrated in the presence of cold hyperreflexia before rigidity develops ? If the suggestions made in this paper are correct both answers should be positive. The current use of cold anaesthesia may enable the proposition to be tested.

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CONGENITAL HEREDITARY VERTICAL NYSTAGMUS

BY

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Duke-Elder (1949) states that congenital nystagmus varies considerably in extent, direction, and rapidity of the movements. In most cases it affects both eyes equally, but in a few instances it is uniocular. Typically the movements are pendular in type, horizontal in direction, and do not alter on lateral deviation, although they may then become jerky in type. Sometimes the movement is coarser to one side than the other, in which case the head is habitually turned to place the eyes in the position at which the nystagmus is least. In 1911, Nettleship reviewed nine pedigrees of congenital hereditary nystagmus and to this he added four more which he had examined personally. Hemmes (1926) published a pedigree and reviewed all published pedigrees up to 1924, 38 in all. Since then Yawger (1917), Cox (1936), Glover (1937), Waggoner and Boyd (1942), and Rucker (1946) have added their contributions. A careful study of the published reports has shown, with two exceptions, that the nystagmus has been bilateral and horizontal in all cases. Posey (1902) described a native boy, aged 8 years, who had bilateral vertical nystagmus. The time of onset was not known, but oscillations of the head, of a rotary type, began at 5 years. Three siblings were normal and there was no family history of abnormal eye movements. Walsh (1947) states that the nystagmus is usually horizontal, although torsional nystagmus has been observed by Ohm (1938). It would appear, therefore, that congenital nystagmus of the vertical type is rare. This condition is of great interest to the geneticist and it is for this reason that these cases are recorded.

The family described here is of pure Italian extraction and the nystagmus involves five cases spread over three generations ; three males and two females. The diagrammatic pedigree is set out in the Appendix. Twelve members of the family have been examined and their blood groups and eye colours, etc., are recorded also in the Appendix. There is no known consanguinity in the matings.

Case Reports

Case 1 (II 6).—A male aged 67 years had shaking movements of the eyes and head which were thought to have begun at 3 years of age, following a series of convulsions. The nystagmus is binocular, synchronous, and vertical in type and the movements are coarse and pendular. Approximately 70 oscillations occur per minute. This rate is unaffected by fixing or looking to either side. Visual acuity is normal. The oscillatory movements of the head were absent at the first three examinations, but at the fourth the movements were rotary in type, and could be controlled voluntarily. The number of oscillations varied from 20 to 40 per minute. During fixation they tend to diminish in frequency and increased when the patient was not concentrating.

Case 2 (III 7).—In a male aged 38 years nystagmus and head movements were noticed shortly after birth. On examination, the nystagmus and head movements have the same features as Case 1. Visual acuity is normal. This patient says he can see the eyes shaking in Cases 4 and 5 but not in Cases 1 or 3. He has no difficulty in observing the head movements in the other cases.

Case 3 (IV 10).—In a female aged 15 years nystagmus has been noticed since birth. Head movements started early in infancy and disappeared at 8 years. The nystagmus is binocular, synchronous, and vertical with an approximate rate of 140 to 160 oscillations per minute. The movements are pendular and of moderate amplitude. Visual acuity is normal and there are no errors of refraction. This patient could see the eyes shaking in Cases 1 and 4 but is unable to appreciate this in Cases 2 and 5. Head movements are easily observed. The position of the head is normal.

Case 4 (IV 13).—In a male aged 10 years nystagmus and head movements were noticed since birth. The nystagmus is similar to Case 3, except that the rate is approximately 130 oscillations per minute. Vision is normal and there are no errors of refraction. Rotary oscillations of the head have been observed on several occasions. They are not present all the time and tend to diminish during fixation. When he is not fixing, the oscillations start at a slow rate, approximately 5 to 7 per minute and gradually increase to 30 to 40 per minute. The patient is conscious of these movements and can

stop them in a short time. The head movements disappear during sleep, but the nystagmus persists. It was observed that the head movements cease when the eyes are closed. The patient keeps his head habitually rotated to the right and the occiput slightly depressed towards the left shoulder, so that his eyes are directed somewhat to the left and upwards. The patient is left-handed and his Stanford-Binet I.Q. is 80. This patient was subjected to caloric tests as described by Fitzgerald and Hallpike (1942) in order to determine the function of the labyrinth, but there was no response to these tests.

Case 5 (IV 15).—In a female aged 15 months nystagmus was noticed at birth. The nystagmus is binocular, synchronous, and vertical in type, and the movements are pendular and of very wide range. Approximately 60 oscillations occur per minute. The rate is unaffected by fixing or looking to the side. The nystagmus is unaltered during sleep and there are no errors of refraction in either eye. Up to the present, no abnormal head movements have been observed.

Discussion

Nettleship drew attention to the fact that there seemed to be an association between the head movements and mode of descent in hereditary nystagmus. In some stocks the disease was transmitted by either sex, and affected females almost as frequently as males. This type was frequently associated with oscillation of the head. In another group the nystagmus was limited to males but was directly transmitted only by females and this suggested a sex-linked recessive factor. Oscillations of the head were rare or absent in this group. Glover (1937) described a family in which only males showed the defect and several had head nodding which tended to disappear. Rucker (1946) showed in his pedigree that the nystagmus was inherited as a sex-linked recessive factor and a considerable number of the affected persons had associated head movements. Duke-Elder (1949) subdivides congenital nystagmus into three groups : (*a*) An ambi-sexual irregularly dominant form, affecting both sexes, but males more frequently than females ; frequently there are associated head movements. (*b*) A recessive sex-linked type, which is limited to males ; head movements are not common, but defects in the eyes such as pigmentary failure, red-green colour blindness, and in the central nervous system, e.g., Lebers optic atrophy or spastic paralysis. (*c*) A simple recessive rare form, which is frequently associated with consanguinity in the parentage. The pedigree described in this paper would be acceptable in the first group, except for the vertical nystagmus. It is not possible to draw any conclusions from such a small number of cases, but it would appear that the type of nystagmus is not tied to a particular mode of inheritance. Nettleship (1911), Cox (1936), and Walsh (1947) observed that the nystagmus was less marked during fixation and was increased by looking sideways. In this pedigree fixation and alteration of the visual axis had no effect on the nystagmus. It is interesting that some of these patients were unable to appreciate the nystagmus in others. It was thought at first that the eyes must be synchronizing, but in Cases 2 and 3 this does not seem possible as there was a considerable difference in the rate and amplitude of the nystagmus. Nettleship described a baby with rotary head movements, who died at 5 months of age. The sister, herself affected, was able to recall the head movements, but could not say whether or not the eyes were involved. It is possible that this girl could not appreciate the abnormal eye movements in her brother, and it is therefore important to obtain histories from unaffected members of the family, otherwise several cases may be missed.

Cox was of the opinion that the head movements cancelled the nystagmus in order to steady the retinal image, and refers to Nettleship as having made the same observation. This, however, is not necessarily correct, for according to Nettleship :

> " So far as I have been able to observe, the two movements, when both are present, are in the same plane, both as a rule being horizontal. But whether the rapidity of the head-and-eye movements is the same and their rhythm such that one tends to neutralize the other I cannot say, and I doubt whether accurate information on the point can be gathered unless instantaneous photography or some kind of automatic movement-recorder can be pressed into the service."

In this pedigree and the case described by Posey (1902) the head movements were not in the same plane as the nystagmus, their rate was much slower, and the fact that the movements disappeared makes it difficult to imagine that the head movements were neutralizing or compensating for the nystagmus. M'Gillivray (1895) describes a patient with horizontal nystagmus and head movements, in which the head movements started with a nod, then rotation to the left, and this was followed by an upward movement with the result that the head movements roughly described a circle. In the other five cases the nystagmus was more rapid than the rotary head movements. M'Gillivray observed that the head movements were more active during fixation and Nettleship and Cox observed this in some of their cases. In this series the movements diminished during fixation and increased whilst gazing abstractedly. Case 2 volunteered the information that he was more conscious of the head movements while concentrating and he tried to suppress them as soon as they appeared.

The actual site of the lesion in congenital hereditary nystagmus is unknown as none of the cases have come to post-mortem study. Peripheral failure of fixation was suggested as an aetiological factor, but this could only apply if the nystagmus began after the first month, i.e., when the normal infant begins to fix. Nettleship (1911) describes cases where the nystagmus was present at birth and to this may be added Cases 4 and 5. Posey (1902) discussed his case with Professor W. G. Spiller (Philadelphia), who suggests that the vertical nystagmus might be due to weakness in the ocular muscles and that the lateral head movement might be due to slight left sterno-cleido-mastoid muscle weakness. Yawger (1917) referred his case to Dr. Alexander Bruce (Philadelphia), who suggested that Deiter's nucleus might be the site of the lesion. Nettleship (1911) suggests that there may be a congenital lack of pigmentation of the retinal epithelium in the region of the macula. Walsh (1947) observed several negro families with hereditary nystagmus where pigmentation could scarcely be a factor. Hemmes (1926) thought that the nystagmus was due to a disturbance of the function of the otoliths. Duke-Elder (1949) thinks that anomalies may exist in the vestibular tracts and centres, or in the connexions between these centres and the oculo-motor nuclei, as well as a disturbance in the labyrinthine mechanism. It is impossible to say whether or not the labyrinths are normal in these cases, but Case 4 did not respond to the caloric tests. An unaffected member of the family gave a normal response.

Summary

Five cases of congenital hereditary nystagmus have been described. They are unusual in that the nystagmus was vertical in all, and in three patients the head movements were rotary in type. Linkage data are presented.

I would like to thank Professor F. M. B. Allen for permission to study these cases and Professor A. C. Stevenson for his helpful advice and criticism.

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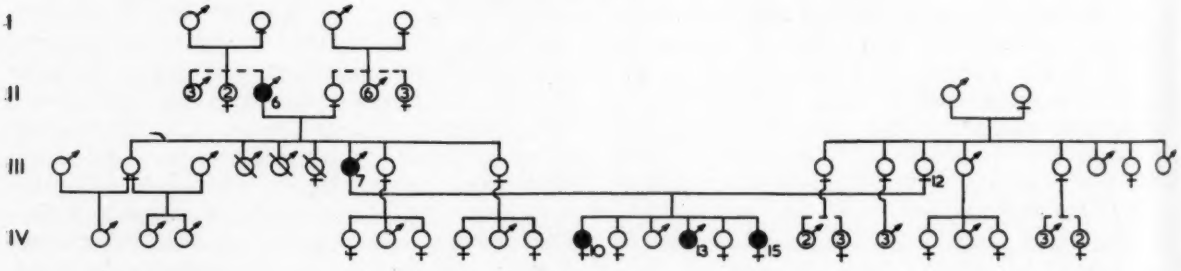
APPENDIX

VERTICAL NYSTAGMUS



LINKAGE DATA

Chart Ref.	Birth Date	Sex	Seen	Affected	Taste	Colour Vision	ABO	M.	N.	S.	Rh	P.	Eye Colour
II 6	1887	M	Yes	Yes	+	+	A_1	−	+	+	R_0r	+	Blue
II 7	1894	F	Yes	No	−	+	A_1	+	+	−	R_1R_1	+	Brown
III 2	1911	F	Yes	No	−	+	A_1	+	+	+	R_1R_0	−	Brown
III 7	1916	M	Yes	Yes	−	+	A_1	−	+	+	R_1R_0	+	Brown
III 8	1917	F	Yes	No	+	+	A_1	+	+	−	R_1R_0	+	Brown
III 9	1918	F	Yes	No	+		A_1	+	+	+	R_1R_0	+	Brown
III 12	1915	F	Yes	No	−	+	0	−	+	−	R_1R_1	+	Brown
IV 10	5.4.39	F	Yes	Yes	−	+	0	−	+	−	R_1R_1	+	Brown
IV 11	1941	F	No	No	−	+							Blue
IV 12	3.2.43	M	Yes	No	−	+	A_1	−	+	+	R_1R_1	−	Blue
IV 13	1.5.44	M	Yes	Yes	−	+	0	−	+	+	R_1R_0	−	Brown
IV 14	23.12.48	F	Yes	No	−	+	Refused blood examination						Blue
IV 15	24.8.53	F	Yes	Yes	?	?	A_1	−	+	+	R_1R_1	−	Blue

J. Neurol. Neurosurg. Psychiat., 1955, **18**, 199.

A BENIGN "TUMOUR" OF THE CEREBELLUM

REPORT ON TWO CASES OF DIFFUSE HYPERTROPHY OF THE CEREBELLAR CORTEX WITH A REVIEW OF NINE PREVIOUSLY REPORTED CASES

BY

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It sometimes happens that a patient shows clear signs of an expanding lesion in the posterior cranial fossa, but at operation no neoplasm can be found. The cerebellum may appear vaguely abnormal, but biopsy is inconclusive, except for the fact that the tissue is not gliomatous. One possible cause of this occurrence is a condition in which the neural elements of the cerebellar cortex undergo certain characteristic changes resulting in an increase in bulk of some part of the organ, and hence in the clinical picture of a posterior fossa tumour. The pathological nature of these changes, which are remarkably constant from case to case, is still not certain. It is probably not neoplastic, though the previous authors who have described the condition are not agreed on this.

Two cases of this condition are described here, with case histories and pathological findings. An account is also given of nine previously reported cases, all showing a similar pathology, and a tenth showing a somewhat different picture, which, there is reason to think, may represent an earlier stage of the same disease. Of these 12 cases, three died from the progress of the disease; five died during or shortly after operation; two died from other causes; and the remaining two were successfully operated upon.

The first of the two cases to be reported on is the second in the series to survive operation. On that account, it is thought worth while to describe his vicissitudes in some detail.

Case Reports

History.—The patient, S. S., was a 52-year-old Jewish labourer. Eighteen months before admission he had the first of a series of episodes of sudden, severe bifrontal headache of a stabbing quality, accompanied by profuse sweating, loss of vision, and a sudden weakness of the legs, which buckled under him. Apparently he did not lose consciousness. Vision returned after a few minutes, and he would be well and fit for work after a short rest. There was no feeling of dizziness; there were no convulsive movements and no incontinence of urine. Similar attacks occurred at the rate of two or three a week for the following four months. There was no headache apart from the attacks.

In October, 1952, he was investigated in another hospital, where he was found to have papilloedema with haemorrhages in both retinae, impaired visual acuity, and constriction of the peripheral visual fields; there was nystagmus on lateral gaze to both sides, but no other cerebellar signs were observed, nor any evidence of long tract damage. Lumbar puncture showed a pressure of 300 mm. of water; the fluid was clear, and contained two lymphocytes per c.mm. and 55 mg. of protein per 100 ml. Ventriculography was proposed, but the patient demurred, and was discharged.

There were no further attacks until the last few weeks before admission to the Maida Vale Hospital in September, 1953, during which the patient had felt weak and collapsed three times, but did not lose vision. On the other hand, headaches, unassociated with attacks, were becoming more frequent, and were occurring two or three times a week, usually in the early morning. Their quality was still sharp and stabbing, but the site had shifted from the forehead to the left temple and back of the head. Only once was there an associated nausea and retching.

Other symptoms had appeared over the preceding few months. Feeling had been impaired in the right hand, starting with the thumb and spreading to the other fingers, and the patient was having difficulty in fine movements such as fastening buttons. Several times the right hand had trembled uncontrollably for a few seconds, and had once gone into spasm in a clutching attitude. Further, the patient complained of gradually failing vision and hearing over the past year or two, and of increasing difficulty—his wife confirmed this—in day-to-day memory. The wife added that he had "grown old" in the last year or two; otherwise there was no clear history of mental deterioration. There were no other symptoms.

On admission, the positive physical findings were a blood pressure of 160/105 mm. Hg; some slowness of comprehension but otherwise no definite mental change; bilateral papilloedema with haemorrhages; a visual

acuity of 6/36 on the right and 6/12 on the left, both corrected, and a fairly uniform constriction of the peripheral visual fields on both sides ; lateral nystagmus, more marked to the right ; some deafness, of middle ear type, more marked on the right ; a little intention tremor and dysmetria of the right hand, with impairment of quick alternating movements on that side ; slight impairment of skin sensibility, of two-point discrimination, of vibration and position sense, and of stereognosis in the right hand ; gait was steady, and there were no signs of pyramidal damage.

Plain radiographs of the skull showed only doubtful thinning of the dorsum sellae. The internal auditory meatuses were normal. Electroencephalography gave a record suggestive of a tumour in the posterior fossa, and tests of labyrinthine function, performed by Mr. W. S. McKenzie, pointed to a right-sided cerebellar lesion.

Ventriculography was performed on October 21. Pressure was high, and the films showed a fairly gross hydrocephalus involving the lateral and third ventricles. The fourth ventricle was dilated and shifted upwards and to the left, indicating a low right-sided cerebellar tumour.

The ventricular fluid was quite normal.

On the same day, Mr. Valentine Logue explored the posterior fossa through a right occipital flap. No tumour could be seen arising from the meninges or in the cerebello-pontine angle, and none was felt on needling the cerebellum ; on the other hand, the right cerebellar tonsil was grossly enlarged, herniating into the foramen magnum, compressing and indenting the medulla, and blocking the outlet of the fourth ventricle. The lamellar pattern appeared normal, though the folia were uniformly thickened. The surface of the cerebellum was unusually pale. Small incisions were made in its substance without revealing anything more than a slightly irregular firmness of the cerebellar white matter. A small piece was taken for biopsy. Closure of the dura was not practicable, owing to bulging of the cerebellum, and the patient was left with the decompression and external ventricular drainage, which was continued for seven days.

In the biopsy specimen the most striking feature was the condition of the small blood vessels. These showed a generalized proliferation, especially immediately below the pia, but also in the underlying tissue. In two places this amounted to angiomatous nodules, visible with the naked eye (Fig. 1). The vessel walls were diffusely calcified. The pia itself was thickened, and in places folded double in deep clefts in the nervous tissue. This tissue was quite unlike normal cerebellum. Immediately below the pia there were myelinated nerve fibres and a number of glial nuclei. Beyond this there were patches containing nerve cells of various shapes and sizes, but none were characteristic of the cerebellar cortex. The picture was not considered to be a neoplastic one ; further than this, with the limited material to hand, it was not possible to go.

After a week, during which the patient's condition was satisfactory, with virtually unchanged neurological signs, ventriculography was repeated. This showed

FIG. 1 (S. S.).—Angiomatous vessels, with calcareous incrustations, in thickened pia. H. & E. × 40.

nothing new. After this, the patient's condition deteriorated sharply ; he became drowsy, confused and disorientated, sweated copiously, and developed retention of urine. During the next few weeks he slowly recovered his equilibrium ; cerebellar signs were becoming less obvious, and there had been a complete recovery of the sensory deficit in the right hand. Vertebral arteriography on November 18, 1953, showed that the medulla was still displaced to the left, and that the right posterior inferior cerebellar artery was larger than normal, but there was no sign of tumour vessels.

Meanwhile the occipital decompression began to bulge ; the patient suffered frequent headaches, and repeated ventricular and lumbar taps showed a high and mounting pressure, and it was decided to re-explore.

On November 27, a full cerebellar flap was turned, and a larger exposure obtained. Again no neoplastic mass was found, but the medulla was still compressed and displaced to the left by the huge, herniating right tonsil, and the outlet of the fourth ventricle was blocked, partly by an oversized posterior inferior cerebellar artery. In order to relieve the obstruction, the offending tonsil was amputated at its base and the opening of the fourth ventricle enlarged. The dura was then closed with the aid of a patch of the lining membrane of the sac which had formed beneath the neck muscles. The pathological description of the excised tonsil will be deferred to the next section.

The patient was up and about after two weeks, during which there were episodes of mental confusion, retention of urine, troublesome hiccups, and irregular pyrexia.

Over the next two months the patient's condition gradually improved, though at first there was some unsteadiness in walking, with a tendency to stagger to the right. There were no further headaches, and the patient felt fairly well. However, the meningocoele in the neck reasserted itself. Lumbar punctures were frequent, and consistently yielded a yellowish fluid containing several hundred cells (many of them histiocytes) and 300 to 500 mg. of protein, with a pressure of

about 180 mm. Clearly the cerebrospinal circulation was still inadequate, and it was decided to perform a short-circuiting operation.

Ventriculography on January 27, 1954, showed a dilated, but now centrally situated, fourth ventricle. A right frontal flap was turned, and an anterior ventriculostomy was performed, using a short length of 2 mm. bore polythene tubing.

Post-operative progress was uneventful. The neck swelled once more, but after 250 ml. had been withdrawn, and a pressure bandage applied, it remained flat.

The patient was discharged on February 10, 1954, feeling a good deal better than when he came in, and with no particular symptoms. He had lost four of his 17 stones, and the blood pressure was 130/80 mm. Hg. He failed dismally in simple arithmetic tests, and was slow in comprehension, as he had been before; otherwise he was rational and at home in the world. Both vision and hearing had improved. Papilloedema had subsided, leaving signs of optic atrophy on the right. There were virtually no cerebellar signs.

Fourteen weeks later he was seen as an out-patient, having been working as a manual labourer for three weeks. Mentally, he was more alert, and performed arithmetical tests readily. The optic discs were flat, and vision in both eyes had improved. There was no nystagmus, or any other sign of cerebellar damage. The only symptom was a recurring pain (apparently of muscular origin) in the back of the neck.

A year later (13 months after the final operation) this symptom had largely cleared; otherwise, the patient's condition was virtually unchanged.

Pathological Findings.—On naked-eye inspection, the excised tonsil showed recognizable cerebellar foliation, but the folia were abnormally broad, and the colour unusually pale. On section, the medullary centre was seen to be lacking, so that the tissue appeared as a much-folded sheet, 1 to 2 mm. thick, with a pial covering on one surface. Without this, there would have been difficulty in distinguishing between the inner and outer surface of the tissue (Figs. 2 and 3).

The structure of the main tissue was uniform almost throughout. It contained two clearly defined layers of approximately equal thickness—an outer one consisting mainly of nerve fibres, and an inner one composed mainly of nerve cells of unusual types. Since no normal cerebellar tissue was included in the specimen, these layers could not be identified with the molecular and granular layers, though the findings in other reported cases make this identification probable.

No lining membrane could be seen on the inner surface of the tissue. In places where the convex aspect of a fold was on the outside, a few strands of nerve fibres, mixed with glial elements, could be seen separating the infolded cellular layers; elsewhere, there were narrow clefts containing blood. Where the convexity of a fold lay inside, the cellular layer stopped abruptly, forming a fairly smooth edge. As in the first biopsy, proliferation of small blood vessels was observed, with basic-staining granules studded along their walls.

Stains for myelin and silver impregnations displayed a fairly uniform disposition of the fibres in the outer layer. These could be seen arising from the cells in the inner layer, running vertically outwards, singly or in small bundles, branching, and thereafter running parallel to the surface along the direction of the folia (Fig. 4). Thus, in sections taken along a folium, there was a criss-cross effect, while in sections taken across a folium one saw mainly vertically-running fibres with

FIG. 2 (S. S.).—Section of excised tonsil. Loyez. × 3. The myelinated layer (dark) has a pial covering. Except for a small area on the left, the central white matter has disappeared.

FIG. 3.—Enlargement from Fig. 2, showing pial covering of myelinated layer. × 30.

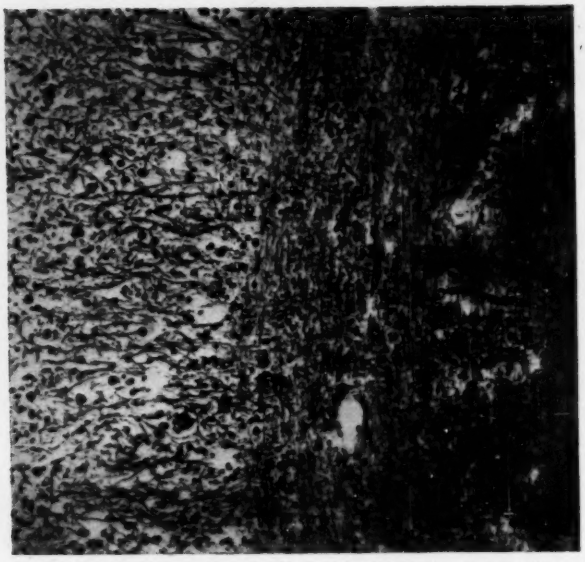


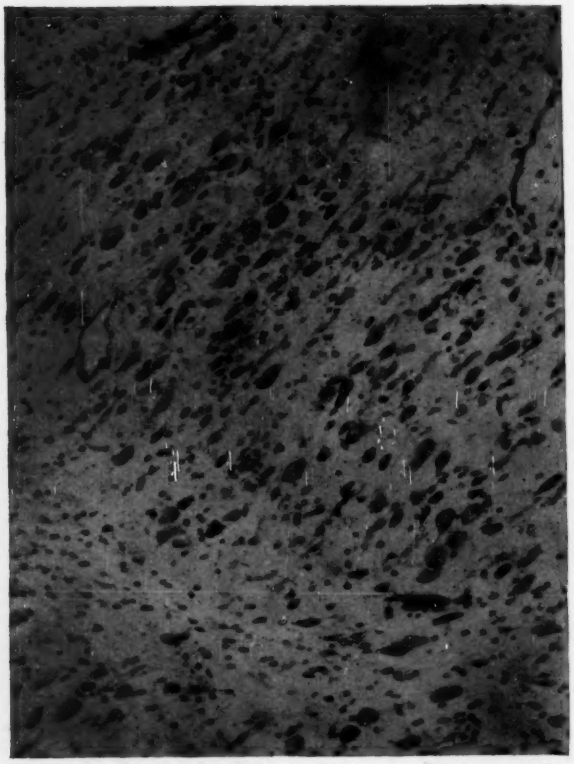
FIG. 4 (S. S.).—Arrangement of fibres in cellular layer (on left) and myelinated layer (on right). Bielschowsky. × 70.

a stipple of cross-cut fibres between. The fibres were of varying thickness, and a large proportion were myelinated. Nothing resembling Purkinje dendrites was seen. This layer also showed glial nuclei, mainly rounded, about 6μ in diameter, greatly in excess of the number usually found in the molecular layer. In places, these cells occurred in closely packed clusters, elsewhere in short chains, an arrangement typical of oligodendrocytes. Their presence can be confidently related to the presence of myelin sheaths in this layer. A few isolated nerve cells were seen, similar to those found in the inner layer. Small blood vessels were abundant, many showing basophilic incrustations, which were shown by von Kossa's method to consist of calcium salts.

The cells which composed the bulk of the inner layer, though they showed much variation in size, shape, and staining properties, were for the most part clearly identifiable as nerve cells (Figs. 5 and 6). The cell bodies were round or polygonal, the larger ones up to 45μ in diameter, the smaller ones about 8μ, and averaging about 16μ. Many of them had long, tapering cytoplasmic processes, ending in a thick fibre. Nuclei were round, sausage-shaped, or indented, and averaged about 10μ in diameter. The cell bodies contained Nissl substance; the nuclei contained a little chromatin, and well marked, usually eccentric nucleoli. In some places there were many degenerate-looking forms, some with diffusely dark-staining cytoplasm, others with what appeared to be nuclear inclusion bodies alongside the darker-staining nucleoli (Figs. 7 and 8). Occasional dumb-bell cells with two nuclei were seen, but there were no mitotic figures.

The fibres arising from these cells, many of which were very thick, ran in an irregular network between the cells before collecting into small bundles which passed vertically into the outer layer.

Glial nuclei were present in the inner layer, but not so abundantly as in the outer one. In addition, there were



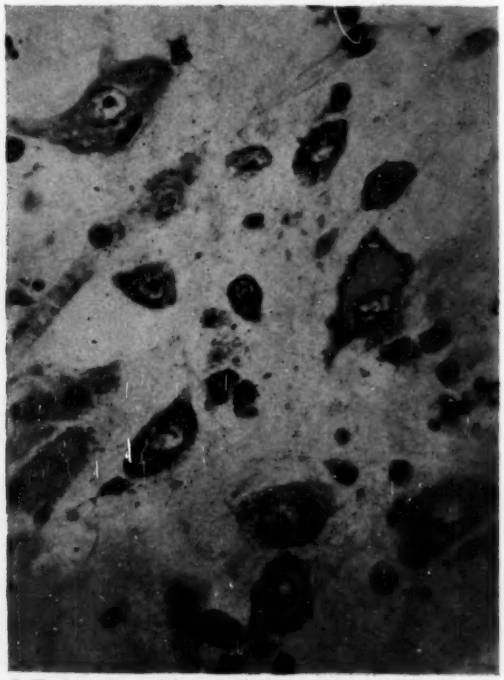


FIG. 5 (S. S.).—Top right: radially arranged glial nuclei in outer layer. Lower left: remains of white lamina. Between: layer of nerve cells. Nissl. × 70.

FIG. 6 (S. S.).—Group of nerve cells. Nissl. × 280.

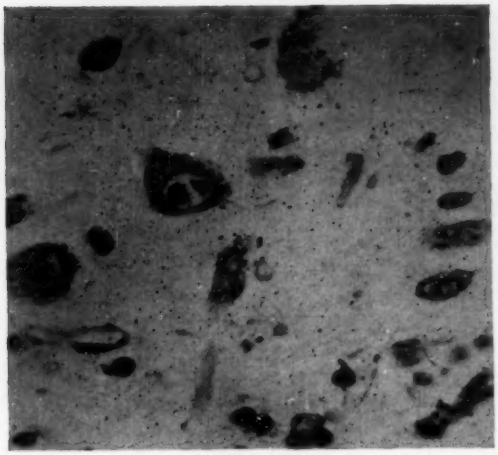


FIG. 8

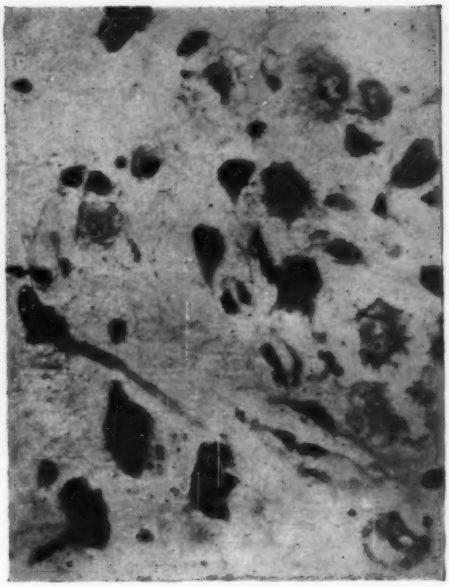


FIG. 7

FIG. 7 (S. S.).—Cell degeneration in the inner layer. Nissl. × 280.

FIG. 8 S. S.).—Cells of inner layer, one containing a nuclear inclusion body. Nissl. × 280.

occasional very large cells (up to 90μ in diameter), seemingly of glial type (Fig. 9). These probably correspond to the Alzheimer cells observed by Bielschowsky and Simons (1930) in one of the cases which they describe. Specific staining for glial fibres revealed a mild gliosis in one or two places in the outer layer, and again in the clefts which corresponded to the vanished medullary centre.

In the inner, cellular layer one occasionally saw small, deeply staining nuclei which closely resembled those of normal granule cells : otherwise, these elements were totally lacking, except for one small area where granule cells were abundant, forming a thin but recognizable layer. Within this there was a medullary centre of reasonable thickness ; and at the margin between the granule-containing layer and the myelinated outer layer, there were appearances suggestive of basket-formations surrounding empty pockets, where one might

FIG. 10

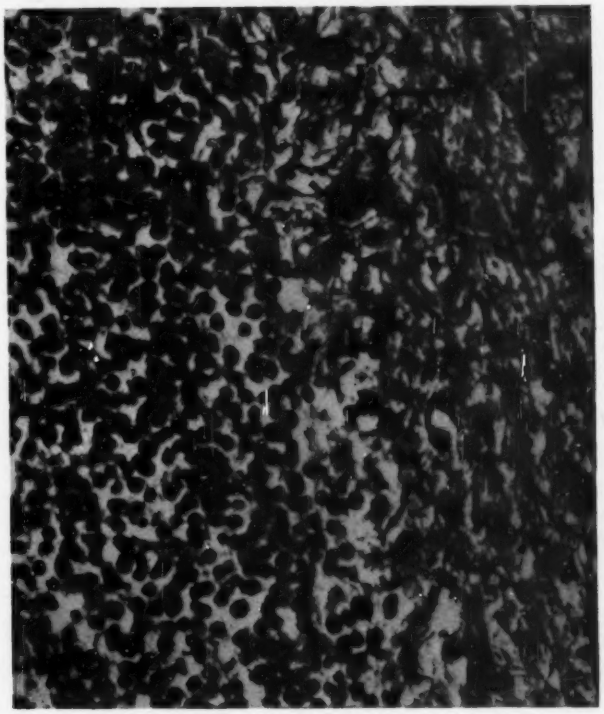
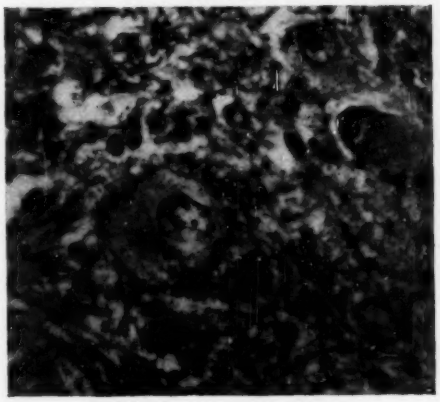


FIG. 9 (S. S.).—Large cell, probably of glial type ; two nerve cells on right. Loyez. × 280.

FIG. 10 (S. S.).—Area containing granule cells, and suggestion of empty basket formations. Bielschowsky. × 280.

FIG. 9



fancy Purkinje cell bodies to have been (Fig. 10). Unfortunately, it was not possible to trace the transition from this comparatively normal area to the abnormal one.

The material for the second case was supplied by the kindness of Mr. W. R. Henderson.

History.—The patient, J. D., was a man of 21, who presented in January, 1950, with a five-month history of vertiginous attacks, during one of which he fell forwards and could not get up. For three months there had been attacks of blurring of vision, which were becoming more frequent; for two months, occasional unsteadiness of gait, occasional tinnitus, one attack of vomiting, but no headache. On examination, he had severe bilateral papilloedema, and slightly impaired vision on the left, and no other physical signs. A diagnosis of posterior fossa tumour was made, and an exploration was undertaken. The patient died shortly after the operation, probably as a result of accidental damage to the brain-stem.

Pathological Report.—Necropsy showed no abnormality outside the brain. Here there were signs of raised pressure—flattened cerebral convolutions, moderately dilated lateral ventricles, and tonsillar herniation—and a good deal of subarachnoid blood.

Externally, the cerebellum showed relative enlargement of the right hemisphere. Foliation was of more or less normal pattern, but in some areas on the right the folia were increased in breadth, up to about twice the normal size. This was most marked in the area behind the fissura prima on the tentorial surface (Fig. 11). Nothing abnormal was seen in the superficial blood vessels.

The cut surfaces showed a normal cerebellar pattern on the left. On the right, the lateral part of the hemisphere showed a thickened (2·5 to 3·5 mm.) folded cortex, paler than normal cortex, devoid of central white matter, and therefore unconnected with the white matter surrounding the cerebellar nuclei. After two parallel cuts, this abnormal tissue fell away readily from the main block. The white matter, which was less in quantity than on the left, appeared to be connected only with normal areas of cortex. The midline of the vermis was shifted half a centimetre to the left, and there was a corresponding distortion of the brain-stem (Fig. 12).

Blocks were cut for sectioning from the brain-stem, from the area containing the cerebellar nuclei, and from both hemispheres, including a "transitional" area on the right. Nissl, Weil, and Bodian stains were mainly used.

The histology of the frankly diseased tissue corresponded closely with that of the previous case, except that the blood vessels in this case appeared normal. There was, as before, a cortex about 2 mm. thick, clearly divided into an outer layer, consisting of myelinated and non-myelinated fibres, and an inner layer of abnormal nerve cells, with no underlying white matter (Fig. 13). The fibres in the outer layer, as before, left the inner layer in small bundles and coursed first radially then horizontally along the folium (Fig. 14). A few nerve cells were seen in the outer layer, but glial nuclei were not present in excess, and no "chains" were seen. The cells of the inner layer were similar to those in the first case, with diameters of 8 to 35μ, averaging about 12μ, and included a rather larger proportion of tadpole-shaped forms (Fig. 15). No mitotic figures were seen.

The area of transition from normal to abnormal cortex (Figs. 16 and 17) showed special features. First, there were signs of myelination in fibres of the innermost part of the molecular layer, running horizontally and at right angles to the folium, which were accordingly identified as basket-cell fibres; also in fibres running in the direction of the folium in the outermost part of the molecular layer, these being identified as granule cell fibres. A similar picture was found in one or two places on the left side (Fig. 18).

The cells themselves appeared normal in these areas, and Purkinje cells were present in normal numbers. There were several areas (mostly at the convexity of a folium) where the granular layer was thicker, the granule cell nuclei stained less deeply, and Purkinje cells became sparse. Surviving Purkinje cells showed signs of degeneration, such as "torpedo" formations in their processes (Fig. 19) and in between them were empty basket-formations, which presumably marked the sites of extinct Purkinje cell-bodies. Next, abnormal cells began to appear in the granular layer, and Purkinje cells disappeared; and finally recognizable granule cells disappeared, and all the cells were of the abnormal type. Since other authors, in describing this transition, have regarded the abnormal cells as tumour cells "infiltrating" into the granular layer, it is worth emphasizing that one cannot discern a clear morphological distinction between granule cells and the abnormal types. In the transition area, one can pick out cells forming a concontinuous series from one to the other (Fig. 20).

The changes in the central white matter are not apparent until the transition zone is reached. Here, it becomes considerably thinner, as the cortex becomes thicker, and one must follow the cortex for a considerable distance before the white centre finally vanishes.

Examination of the dentate, pontine, and olivary nuclei showed no definite changes, but it was difficult to compare the two sides on account of the gross distortion of these areas.

Review of Previously Reported Cases

In this section summaries will be given of the individual case histories, on account of their practical interest and of the relative inaccessibility of some of the literature. The pathological findings, which are closely similar, will be summarized together.

Case 1.—This was described by Lhermitte and Duclos (1920) and is believed to be the first reported cases.

Male, aged 36. For one year, hearing impaired on left; for 10 months, occipital headaches. For one month, dizzy attacks, with falling; unsteady gait; mental deterioration, with confusion and loss of memory and

FIG. 11 (J. D.).—View of tentorial surface of cerebellum. Thickened folia can be seen on the right. A portion of the right hemisphere has been cut away. 2/3 natural size.

FIG. 12 (J. D.).—Cut curface, looking rostrally. There is a deep cleft between the diseased tissue on the right and the white matter of the hemisphere. 2/3 natural size.

FIG. 13 (J. D.).—Section of diseased tissue. What appears to be the outside is in fact the inner surface of the cortex. There is a pial lining to the central cleft. Weil. × 3.

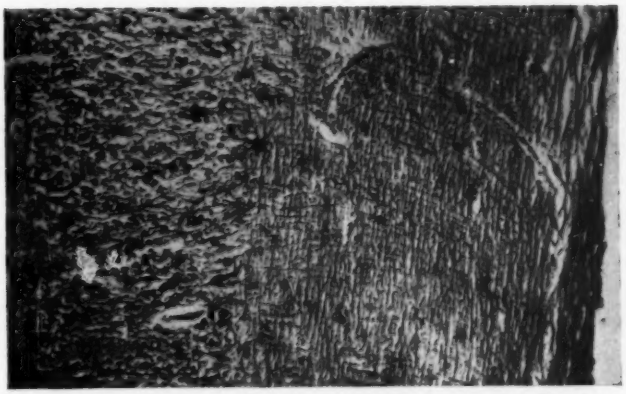


FIG. 14 (J. D.).—The disposition of fibres in the granular layer (left) and the molecular layer (right). Bodian. × 67.

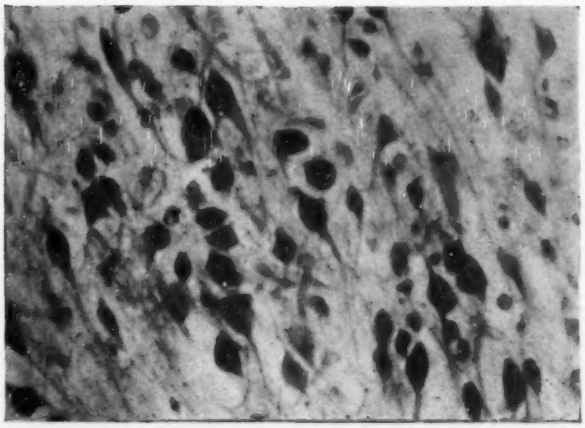


FIG. 15 (J. D.).—Cells in the granular layer. Nissl. × 290.

FIG. 16

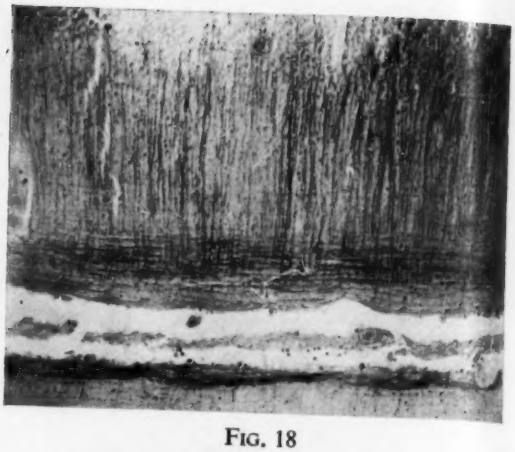


FIG. 18

FIG. 19

FIG. 17

FIG. 20

concentration. On admission, confused, disorientated, dysarthric; gross cerebellar ataxia of four limbs; nystagmus to right and left; tendon reflexes increased. Sensation was normal.

Lumbar puncture showed a normal pressure, with normal cells, but increased protein in the fluid. The Wassermann reaction was negative. After a week, the patient went rapidly downhill, with increasing headaches, vomiting, and mental distress. He died in coma.

Case 2.—This was described in its general aspects by Schmidt (1926). The cerebellum was examined and reported on by Hallervorden, and his findings presented in a paper by Bielschowsky and Simons (1930).

Male, aged 45. Congenital malformation of skull. Ten years before admission sustained a head injury. Unconscious for a day; subsequently had left hemiplegia, which cleared partially. From this time on, subject to headaches and dizzy attacks. Five months before final illness, treated for rheumatic pains in one arm. Observed to have a left facial palsy. Later became bedridden, and was found to have bilateral papilloedema. From this time on, increasing headaches, with vomiting; motor disturbances, with neuralgic pains in right arm and leg. Palsy of left vocal cord and atrophy of left sternomastoid. Increasing marasmus and death from pneumonia.

Case 3.—This case was reported in great detail by Bielschowsky and Simons (1930).

Female, aged 20. Born with six digits on each hand. Ulnarmost digits amputated in infancy. For two years, unsteadiness of gait; occasional dizzy attacks and fainting fits; paraesthesiae in all limbs; some supra-orbital pain; few headaches, never severe; some retching, no vomiting. Unsteadiness getting steadily worse.

Physical findings included bilateral papilloedema, coarse nystagmus on right and left gaze, and well marked cerebellar signs in the limbs, mainly on the right. Radiographs showed evidence of raised intracranial pressure, confirmed by lumbar puncture. The patient was referred for surgery, with a diagnosis of right-sided posterior fossa tumour, but died on the table after the bone had been removed and before the dura was opened.

Case 4.—This case was described by Foerster and Gagel (1933) as one of a series of ganglion cell tumours of the brain.

Female, aged 43. Multipara. Rheumatic valvular disease. For one year, headaches, mainly right frontal. Numbness of right side of face; giddy attacks; vomiting. For two weeks, clouding of vision. Physical examination showed severe bilateral papilloedema, impairment of right trigeminal function and right facial paresis. No cerebellar signs. Three months later, increased papilloedema and visual impairment, but still no cerebellar signs. Ventriculography showed dilated lateral ventricles. After this there was definite nystagmus to the right. Exploration of the posterior fossa had to be stopped after removal of the bone, as the patient went into extensor spasm and stopped breathing for a time. Six days later a second attempt was made. The dura was tense but relaxed and pulsated after ventricular puncture. Opening of the dura revealed a grossly swollen left cerebellar hemisphere, with broad, flattened, greyish-yellow gyri. The whole infero-lateral part of the hemisphere was excised. Respiratory arrest, and death on the table.

Case 5.—Barten (1934) reported this case.

Female, aged 37. For seven years, dizzy feelings when standing up. Unsteady gait, getting worse. Two years later, following third pregnancy, marked increase of unsteadiness, and visual disturbances. Paraesthesiae and transitory weakness in right arm and leg. Eight months later, seen as out-patient; coarse nystagmus, bilateral facial paresis, dysarthria; increased tendon jerks. No papilloedema. Lumbar puncture; pressure normal, fluid normal. During the next few years there was gradual mental deterioration, and the patient was finally brought in, having been bedridden for six months and stuporous and confused for a few days. She had difficulty in swallowing, and had developed bronchitis. She died on the day after admission, from sudden central respiratory arrest.

Case 6.—Christensen (1937) described this case as one of a series of five ganglion cell tumours in the brain. This is her case 5.

Male, aged 34. For six years, attacks of "pressure" feelings on both sides of the head associated with severe pain in the back of the neck, "flickering" in the temporal fields of both eyes, vomiting, and a feeling of weakness in the legs. Attacks occurred about once a month, and lasted about an hour. Over the past year, attacks had become more frequent, and sometimes led to unconsciousness. No symptoms between attacks. Physical signs included bilateral papilloedema, impairment of left trigeminal function, and a mild right facial paresis. There were no cerebellar signs or symptoms. Ventriculography showed a shift of the fourth ventricle and aqueduct to the left.

The posterior fossa was explored. The folia of the right cerebellar hemisphere were thickened and flattened. The consistency of the tissue resembled that of a cerebral glioma, but no definite tumour mass was found. The lateral third of the right hemisphere was resected. Recovery was complicated by a troublesome arachnoiditis, but 18 months later the patient was back at

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FIG. 16 (J. D.).—Section of transition area. Observe (*a*) thickening and altered staining reactions of the granular layer at various points of convexity in the normal area; (*b*) attenuated white matter in diseased area. H. & E. × 9.

FIG. 17 (J. D.).—Transition area. The granular layer in the lower left corner is almost normal, and Purkinje cells are present. Nissl. × 42.

FIG. 18 (J. D.).—Myelinated granule cell fibres in the left hemisphere. The cellular picture in this area is normal. Weil. × 67.

FIG. 19 (J. D.).—Degenerating Purkinje cell near the transition area, showing "torpedo" formation. Bodian. × 290.

FIG. 20 (J. D.).—Mixture of granule cells and abnormal types near the transition area. There are three degenerating Purkinje cells. Nissl. × 290.

work, free from headaches. It has not been possible to trace his subsequent progress.

Case 7.—This case was reported by Heinlein and Falkenberg (1939).

Male, aged 23. Fractured skull as a child ; two days unconscious ; no sequelae. For the past two years, unsteady gait, tinnitus, giddy attacks, feeling of pressure. Symptoms steadily increased. For the past three weeks, severe headache with vomiting, and pain in the back of the neck. Impaired vision in left eye, impaired hearing in left ear. Physical signs included bilateral papilloedema and exophthalmos ; bilateral nystagmus ; impairment of all cranial nerves from 5 to 12 on the left ; and marked cerebellar malfunction, especially on the right. Radiographs showed evidence of raised pressure. A simple posterior fossa decompression was performed but the patient died the following day from central respiratory arrest.

Case 8.—Duncan and Snodgrass (1943) reported this case.

Female, aged 27. Large head since childhood. At age 14, two fingers amputated for cavernous haemangiomata. One and a half years ago, one of two small nodules in scalp, present since birth, quickly grew to size of hen's egg. It was excised and found to be an angioma. From this time, began to suffer from frontal and occipital headaches, which grew steadily worse. Tinnitus in right ear. Later, sudden attacks of weakness, with falling, but no loss of consciousness. For eight months, diplopia and gradually failing vision ; unsteadiness of gait ; attacks of " numbness " in face and elsewhere ; transient attacks of difficulty in speaking.

Physical signs included an unusually big head ; bilateral severe papilloedema, with some loss of visual acuity and constriction of fields ; coarse nystagmus, right and left ; diplopia on looking to the right ; hypoaesthesia on left side of face ; depressed gag reflex on left. Cerebellar signs in the limbs ; right and left dysdiadochokinesia, and reeling, broad-based gait, with tendency to fall to the right.

Lumbar puncture showed a pressure of 400 mm., with a normal fluid. Skull radiographs showed thinning of the dorsum sellae, and ventriculography a symmetrical dilatation of the lateral and third ventricles ; the aqueduct was kinked, and the fourth ventricle shifted forwards. At operation, both cerebellar tonsils were found to be herniating into the foramen magnum. The left cerebellar hemisphere was enlarged, but looked normal otherwise. The brain-stem was compressed, and pushed over to the right. No tissue was removed, and the patient was left with a simple decompression. After the operation she was disorientated ; the temperature rose sharply, and she died the following day.

Case 9.—This case was reported by Alajouanine, Bertrand, and Sabouraud (1951).

Female, aged 26. For eight years, attacks of severe occipital headaches, with vomiting. These remitted for about a year, but returned, with the addition of transient muscular weakness and unsteadiness of gait. Later she developed tinnitus in the left ear, and a tendency to return fluids through the nose. Menstrual periods ceased. The blood Wassermann reaction was found to be positive, but arsenic and bismuth therapy produced no improvement. Three years later the physical signs included bilateral cerebellar ataxia, with nystagmus in all directions, right abducens paresis, palatal palsy, most marked on the right, and a " nasal " voice. Vision and fundi were normal ; sensation normal ; tendon jerks increased, but plantar responses flexor. The C.S.F. was normal, and the Wassermann reaction negative in blood and C.S.F. Symptoms steadily increased, and two years later the ataxia had made walking impossible. All limbs were now hypotonic, but there was bilateral ankle clonus and an extensor plantar response. In addition to the right sixth, the left fifth, seventh, eighth, ninth, tenth, and twelfth cranial nerves were affected, and cerebellar signs were more marked. The fundi were normal, and lumbar puncture showed a normal fluid. Ventriculography was proposed, but the patient suddenly died of respiratory arrest.

Pathological Findings in the Previously Reported Series

Except for one case, the cerebral hemispheres showed no pathological changes apart from non-specific ones such as hydrocephalus and cerebral oedema. In every case there was marked enlargement of some part of one cerebellar hemisphere, and in some cases small patches were observed to be affected in other parts of the cerebellum. The pattern of the diseased folia is generally stated to have been normal, except for increase in their breadth. In most cases the affected areas were observed to be paler than normal.

In every case, cross section showed a fairly even thickening of the cortex, with either a gross reduction or a complete absence of underlying white matter. Where white matter was lacking, many of the authors remark on the great difficulty in distinguishing between the outside and the inside of the tissue, a point which could generally be settled by the presence of pial membrane on one surface only. In one case (Case 4) it seems that the authors actually mistook the outside for the inside ; at all events, if one makes this assumption, their descriptions and their excellent photographs tally in every important respect with the others in the series.

In every case the cortex showed two distinct layers, the outer one consisting mainly of nerve fibres, and the inner one of abnormal nerve cells. Recognizable granule and Purkinje cells were absent. In all cases where the transition zone was examined, it was found that the outer layer was continuous with the molecular layer, and the inner one with the granular layer. In all cases except

one (Case 6, in which specific myelin staining was not performed) myelinated fibres were seen in the outer layer, running radially and tangentially in a criss-cross pattern. In five of the nine cases calcareous (or "pseudo-calcareous") incrustations were observed along the walls of the smaller blood vessels supplying the area.

Regarding the cells composing the inner layer, there is a general agreement that they belong to the ganglion cell series. They contain Nissl substance and have prominent nucleoli, and appear to be giving rise to the fibres which run in the outer layer. Apart from this, they vary greatly in shape and size, even in a single area. Cells with double nuclei or double nucleoli have been seen, but in no case have mitotic figures been observed. In spite of this, the general view, from the original authors onwards, has been that the cells are neoplastic in nature. Bielschowsky, who described the pathology in the greatest detail, regarded the cells as neuroblasts, exhibiting every stage of maturity; and this view has been held by several later authors. None of these, however, has dealt with the difficulty of regarding as neuroblasts cells with well developed, myelinated axons.

Glial elements, where they have been commented on, have usually been described as normal in quantity and character. Bielschowsky, however, observed giant glial cells, of the type described by Alzheimer in Wilson's disease, in Cases 2 and 3.

Bielschowsky and Simons and Duncan and Snodgrass are the only authors who report on the cerebellar connexions. The former found in Case 3 that all three cerebellar peduncles were reduced in size on the affected side, the dentate nucleus was missing on the same side, and the cells of the inferior olive roughly halved in number on the opposite side. Duncan and Snodgrass found the peduncles to be normal in size. (This, and other features in their description, suggest that the disease in Case 8 had not progressed as far as in most of the others.)

Special features were present in some of the cases: thus, Case 2 exhibited leontiasis ossea, with gross overgrowth of the left facial and cranial bones; some evidence of osteitis fibrosa; a carcinoma in the left parotid region, with metastases in the liver, the spine, and the base of the skull; a large central "perithelioma" of the left frontal lobe; a carcinomatous deposit 1 cm. in diameter in the lower part of the left cerebellar hemisphere; and two areas of ectopic cerebellar cortical tissue in the white matter of the front part of the same hemisphere, which was also the hypertrophied hemisphere. Cases 3 and 5 showed some widening of the central canal in the upper part of the cord. Case 3 had polydactyly. Case 5 had an abnormally thin skull. Case 8 had multiple haemangiomata, and an unusually large head, with a brain weighing 1,960 g.

Regarding the nature of the disease, the original opinion expressed by Lhermitte and Duclos (1920) was that it was a combination of a congenital malformation and a ganglion cell neoplasm, possibly arising from precursors of Purkinje cells. They named it "diffuse ganglioneuroma of the cerebellar cortex". Bielschowsky and Simons (1930) were frankly bewildered. They suggested, successively, such terms as "neurocytic blastoma", "hamartoma", "hamartoblastoma", without reaching a decision. After discussing the embryology of the cerebellum, they concluded that the absence of granule cells, which are normally derived from the transitory superficial cortex, and the presence of Purkinje-like cell bodies, presumably derived from the ventricular cell layer, provided the main clue. They therefore suggested that the condition was "an experiment of nature, which shows us how the cerebellum develops when the transitory superficial cortex is lacking, and the construction of the cortex is effected solely from the ventricular germinal material". They were also disposed to relate the condition to the concomitant congenital abnormalities—polydactyly and hydromyelia in Case 3, and leontiasis, heterotopia cerebelli, and tumour proneness in Case 2.

Foerster and Gagel (1933) pointed out the similarity of the cellular picture with that of ganglion cell tumours elsewhere in the brain, and agreed with Bielschowsky and Simon that the condition is neoplastic, probably consisting of cells of the Purkinje family, and arising on the basis of a developmental anomaly. They called it "gangliocytoma with a dysplastic basis". A similar view was held by all the subsequent authors except Duncan and Snodgrass (1943), who broke new ground by pointing out that the course of the fibres in the molecular layer of the diseased cortex is in fact the normal course of granule cell axons. From this, they argue that the abnormal cells, which give rise to these fibres, are hypertrophied granule cells, myelination being a natural consequence of the hypertrophic enlargement of their axons. The abnormal cells seen scattered in the molecular layer, they suggest, may be similarly hypertrophied stellate cells. They do not commit themselves further, and do not explicitly accept or reject the embryological and neoplastic theories. They head their paper "Diffuse Hypertrophy of the Cerebellar Cortex", but finally apply the label "Myelinated Neurocytoma".

Spiegel's Case

Finally, there is a case reported by Spiegel (1920) which, though not displaying all the typical features of the cases hitherto described, is of interest partly because of its analogies with Case 2 and with the second of the cases reported in this paper, and partly because it may conceivably represent an earlier, pre-clinical stage of the same disease.

The cerebellar abnormalities were discovered in the routine necropsy on a man of 22, a victim of pulmonary and intestinal tuberculosis, who had never exhibited any neurological symptoms or signs. There was leontiasis ossea affecting the right side of the skull. The right cerebellar hemisphere was unevenly enlarged, and certain anomalies of the lamellar pattern were observed, which were held to demonstrate an arrested development, the stage of arrest being around the fifth month of intra-uterine life.

Serial transverse sections were taken of the whole cerebellum and brain-stem. These showed (1) at least three areas of heterotopic cortical tissue, containing elements of all three layers, in the white substance of the right cerebellar hemisphere. (2) Enlargement, in all dimensions, of the right hemisphere; both cortex and white matter were increased. (3) In the inner part of the molecular layer, many myelinated fibres running parallel to the surface and at right angles to the folia; these were accordingly identified as basket-cell fibres. (4) A rich network of fibres in the granular layer; the granule nuclei themselves were of normal size (about 4μ diameter) but appeared poor in chromatin, and stained more lightly than usual (these last two findings correspond with what was seen on the left side in our second case). (5) Certain anomalies of cell-grouping; for instance, Purkinje cells were seen scattered in the molecular layer, and occasionally in the granule layer. The size of the Purkinje bodies was normal, about 34 to 48μ in the long axis. (6) Scattered microscopic areas in the left hemisphere showed a similar picture. (7) Abnormalities were found in the cerebellar connexions, both afferent and efferent, including (*a*) local widening of the dorsal layer of the left inferior olivary nucleus. This appeared to be due to increase in the number of intercurrent fibres. The nuclear cells were normal in size and appearance. There were similar changes observed at a few points in the olive on the right. (*b*) Increased bulk of the right restiform body was apparently due to increase in number, not size, of the component fibres. (*c*) Increased width of the right dentate nucleus, analogous to that seen in the opposite olive. (*d*) Increased bulk of the right brachium conjunctivum, from an increased number of fibres.

The brachium pontis and the pons itself were also thickened. The rest of the brain, including glia, meninges, and blood vessels, showed no abnormality.

The author considers that the basis of the condition is a local arrest of normal development, occurring some time during the sixth month of intra-uterine life. He bases this on the abnormal lamellar pattern and on the irregular placing of the Purkinje cells. The hyperplastic features are associated with this, as they commonly are in other cases of developmental arrest, for instance, micro- and macrogyria. For the heterotopia, he suggests two alternative explanations, based on previous work; first, that outward migration of cells from the ventricular cell layer has been cut short, and second, that there has been excessive migration inwards from the embryonic cortical layer, perhaps through the agency of invading blood vessels.

The author quotes evidence that in cases of microgyria the maldeveloped areas correspond to the distribution of individual arteries, and takes the view that anomalies of local vascular development may also have played a part in producing this condition, in spite of the lack of visible vascular changes. This is interesting, in view of the vascular changes which have been observed in many of the cases under review.

Concluding, as he does, that this is a hyperplastic condition, primarily affecting the cerebellum, Spiegel draws particular attention to the associated hyperplasia of the efferent systems (dentate nucleus and brachium conjunctivum), and the more surprising "retrograde hyperplasia" of the afferent systems—inferior olive and pons, and their fibre-tracts.

The principal common findings in the 12 cases under discussion (including Spiegel's case) can be tabulated as follows:

Clinical picture of posterior fossa tumour	11 cases
Local hypertrophy of cerebellar cortex	12 cases
Reduction or absence of central white matter	11 cases
Absence of recognizable granule and Purkinje cells	11 cases
Atypical nerve cells occupying the granular layer and sending axons into the molecular layer	11 cases
Medullated fibres in the molecular layer	11 cases
Calcareous deposits along walls of capillaries	6 cases

The remaining features are summarized in the Table.

Discussion

"Such appearances", as Bielschowsky remarked in connexion with Case 3, "are encountered neither in malformations of the cerebellum nor in infiltrating, expanding blastomas". Nevertheless, he concluded that the tumour in question partook

TABLE

SUMMARY OF CASES DISCUSSED

Case	Authors	Sex	Age	Length of History	Site	Special Features	Progress
1	Lhermitte and Duclos (1920)	M.	36	1 yr.	L. ½ sph.	—	Death from intracranial pressure without surgical intervention
2	Schmidt (1926)	M.	45	? 10 yr.	L. ½ sph.	Left-sided skull deformity, multiple tumours in brain and elsewhere. Heterotopia cerebelli	Died of pneumonia
3	Bielschowsky and Simons (1930)	F.	20	2 yr.	R. ½ sph. and tonsil	Polydactyly. Hydromyelia. Atrophy in contralateral olive	Death on table following bone removal
4	Foerster and Gagel (1933)	F.	43	1 yr.	L. ½ sph.	No cerebellar signs or symptoms	Death on table
5	Barten (1934)	F.	37	7 yr.	R. ½ sph. (upper half)	Thin skull. Hydromyelia	Death from respiratory failure
6	Christensen (1937)	M.	34	6 yr.	R. ½ sph.	No cerebellar signs or symptoms	Alive and well 18 months after local resection
7	Heinlein and Falkenberg (1939)	M.	23	2 yr.	R. ½ sph. and vermis	—	Death from respiratory failure one day after posterior fossa decompression
8	Duncan and Snodgrass (1943)	F.	27	1½ yr.	L. ½ sph.	Multiple haemangiomata. Small areas affected in right hemisphere	Death one day after decompression
9	Alajouanine, Bertrand, and Sabouraud (1951)	F.	26	? 8 yr.	L. ½ sph.	Portion of R. anterior obe affected	Died spontaneously from respiratory failure
	Spiegel (1920)	M.	22	—	R. ½ sph. Small areas on L.	No neurological disturbances. Right leontiasis ossea and heterotopia cerebelli. Hyperplastic picture, with increase in white matter and changes in olives and dentate nucleus	Died of tuberculosis
S.S.	(This paper)	M.	52	2 yr.	R. ½ sph., espec. tonsil	Angiomatous vessels in affected area	Alive and well one year after local excision and ventriculostomy
J.D.	(This paper)	M.	21	5 months	R. ½ sph.	No cerebellar signs	Operative death

of the nature of both, and almost all the subsequent commentators have taken a similar view. The idea of a developmental abnormality seems to have been suggested by the absence of the normal cellular elements of the cerebellum, and the presence, in a more or less regular arrangement, of cells of an abnormal type, while the evidence for neoplasia lies in the recurring clinical picture of an expanding tumour arising in adult life, and the appearance of cells of an "immature", "blastomatous" type, similar to those found in ganglion cell tumours elsewhere in the central nervous system.

The main objection to the "embryological" view is that none of the recognized congenital malformations of the cerebellum seem to afford a likely starting-point for the disease in question. It is, of course, possible that the condition described by Spiegel, and the abnormal myelination observed in the comparatively normal areas in our second case, represent a pre-neoplastic stage of the disease; but there is no evidence that these abnormalities are of embryological origin. This uncertainty about the nature of the postulated hamartoma is illustrated by the fact that whereas Bielschowsky and Simons (1930) suggest that the condition is due to local agenesis of the transitory superficial cortex, Kuhlenbeck (1950), in discussing this among other cerebellar tumours, regards them all as neoplasms arising from abnormally persisting remnants of the same layer.

Another objection is the absence, in the cases under review, of cerebellar disturbances in early life. This, however, can be countered with the well-known phenomenon of functional compensation for loss of cerebellar tissue.

The objections to the "neoplastic" view are more serious; namely, the remarkably orderly behaviour of the cells, which spread out in two dimensions only, and emit processes which all pursue a similar course in the molecular layer.

They do not even give the impression of infiltration in the molecular layer. The absence of mitotic figures is a further argument against neoplasia.

There remains the " hypertrophic " theory of Duncan and Snodgrass (1943). This is simply based on the arrangement of the fibres in the molecular layer, which corresponds precisely to that of normal granule axons. (Further confirmation of this was obtained in the two cases reported in this paper, which showed the horizontally disposed fibres running along, rather than across the length of the folia.) The argument is very persuasive, as it is almost impossible to conceive of truly neoplastic cells being under such strict neurobiotactic control as to mimic exactly with their axons the fibre-pattern of the cells they are replacing. The theory is attractive, too, because it enables one to offer a tentative explanation of most of the changes observed in the diseased tissue. Thus, granule cells are absent, not because of agenesis or destruction, but because they have undergone a hypertrophic change. A normal granule cell has a diameter of 4μ ; in the two cases described here, the abnormal cells have an average diameter of 12 to 16μ. If they are in fact granule cells, this implies an increase in volume of 27 to 64 times, and there is no need to postulate an increase in cell numbers to account for the greatly increased thickness of this layer ; in fact, one must suppose that there has been a large-scale disappearance of cells. The increased thickness of the molecular layer can similarly be attributed to the increase in calibre and partial myelination of the component fibres, without increase in their numbers.

There are one or two objections to the " hypertrophic " theory. One is that the cells in question look wholly unlike granule cells. This would be weightier if we possessed the knowledge enabling us to predict what a hypertrophied granule cell ought to look like. In any case, the difference is not much more striking than the difference between normal microglia and compound granular corpuscles. A more serious objection is that many learned authors have described the cells, in no uncertain terms, as neuroblasts of various degrees of maturity. It is only fair to point out that in so doing they are not merely describing the cells ; they are also interpreting them, and drawing implicit conclusions about their origins and destinies, which it would be very hard to substantiate. Bielschowsky himself was clearly unhappy about the idea of a neuroblast with a well developed, myelinated axon. Again, the fact that these cells are closely similar to those found in ganglioneuromas elsewhere in the brain may point in one of two directions. It would be worth while re-examining some cases of this condition, to see whether a hypertrophic theory might not fit them as closely as a neoplastic one.

A feature for which none of the previous authors has offered an explanation is the reduction or disappearance of the central white matter. It might be supposed that this was an effect of the increased pressure in the posterior fossa, analogous to the preferential loss of cerebral white matter in hydrocephaly. Against this is the fact that in the molecular layer " white matter " has actually appeared and increased in width. Another possibility is that the centrifugal and centripetal fibres which compose the white matter are adversely affected by the changes occurring in the granular layer, through which they all pass, and undergo Wallerian and retrograde degeneration in consequence. The same mechanism might account for the disappearance of Purkinje cells, which can be thought of as decomposing as a result of destruction of their axons. These cells seem to be particularly sensitive to adverse conditions, and are the first to disappear, for instance, in ischaemic lesions of the cerebellum.

The finding, in several of the reported cases, of degenerating Purkinje cells and empty basket-formations in the " transitional " areas strongly suggests that the disappearance of these cells is secondary to the other changes taking place, rather than that they are congenitally lacking. The appearances in the transitional area in our second case also argue against Christensen's (1937) view that the tumour is a " Purkinjeoma ". Here one sees a continuous gradation of cell types in the granular layer, from normal granule cells to the abnormal types, but nothing resembling a Purkinje cell, with its characteristic dendrite formation, can be seen. The fact that many of the larger abnormal cell bodies have similar staining properties to those of Purkinje cells is probably without significance. The appearance of a cell body and its nucleus presumably reflects the cell's metabolic behaviour, whereas the manner in which it disposes its long processes would seem to be a far more fundamental characteristic of a particular species of nerve cell.

Since the disease has the clinical features of a progressively enlarging tumour, it is reasonable to suppose that it proceeds by horizontal spread from one or more centres in the cortex. If this is so, the " transitional " areas represent the lines along which normal is being transformed into abnormal cortex and one can reasonably regard the changes observed in following the cortex from a normal to an abnormal part as indications of the

changes which occur in time as a given bit of tissue is overtaken by the disease. On this assumption, the earliest visible change is the myelination of basket and granule cell fibres; next, increase in size and changes in staining properties of granule cells; next, degeneration of Purkinje cells, which finally disappear, leaving empty basket-formations behind them; next, gross hypertrophy of the granule cells and their processes; and lastly, the thinning-out and disappearance of the central white matter.

Whether Spiegel's case showed an early stage of the same disease is difficult to decide. The reasons he gives for regarding the condition as a hyperplasia are not wholly convincing; some of his observations tally with the "early" changes in our second case; and the conjunction of leontiasis ossea, heterotopia cerebelli, and cerbellar hypertrophy, which was also present in Case 2 of the reported series, is very striking.

If the hypertrophic theory is correct, we still have the difficulty of finding a reason for the hypertrophy. At present, there is no clue to an underlying cause, with the possible exception of the changes which have in most cases been observed in the small blood vessels of the region. These seem to have been most marked in our first case, which showed small angiomatous masses at several points. Calcification in capillary walls is found in other conditions, and it is quite possible that the vascular changes are in fact secondary to the changes in the tissue they supply. The fact that several of the patients have shown congenital abnormalities in other parts of the body has been taken by some authors as evidence that the disease is genetically determined; but there is no constant feature in the observed aberrations of development, and in over half the patients no such abnormalities were discovered. A genetic cause is, however, a possibility, and should be considered along with the other possibilities, such as neoplasia or even a virus infection.

On the question of diagnosis and treatment there is not very much to say. There appears to be no clinical feature by which the condition can be distinguished from other posterior fossa tumours; on the other hand, it should be readily recognizable in the course of a cerebellar exploration, from the appearance of pale, expanded folia, and the absence of a definite neoplastic mass. It is worth noting that whereas the rapid examination of frozen sections from a biopsy specimen would probably provide a clear answer, a smear biopsy would not. The correct treatment would seem to be an excision of the diseased part, if (as is the case with the tonsil) it is surgically accessible, and relief of the obstructive hydrocephalus by some short-circuiting procedure such as anterior ventriculostomy.

As to nomenclature, the term "diffuse hypertrophy of the cerebellar cortex", suggested by Duncan and Snodgrass, seems to fit the case without begging any questions.

Summary

Reports are given of two cases of diffuse hypertrophy of the cerebellar cortex, with clinical histories and pathological findings.

A review is given of nine previously reported cases of the same condition, and of a tenth, which is believed to display an earlier stage of the condition.

The nature of the disease is discussed, and reasons given for believing that it is of a hypertrophic rather than of a neoplastic type.

Some remarks are made on diagnosis and treatment.

I wish to express my thanks to Dr. W. H. McMenemey, pathologist at the Maida Vale Hospital, for his continuous interest and help in preparing this paper; to Mr. W. R. Henderson, of Leeds, for his kindness in making available the material for the second case; to Sir Russell Brain, under whose care the first case originally came, and to Mr. Valentine Logue, the surgeon in charge of the case, for their help and encouragement; and to Mr. Gordon Cox and Mr. Frank Blackwell for their valuable technical assistance.

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J. Neurol. Neurosurg. Psychiat., 1955, **18**, 214.

DYSPHASIA FOLLOWING RIGHT TEMPORAL LOBECTOMY IN A RIGHT-HANDED MAN

BY

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It is well known that excisions of parts of the right hemisphere very seldom occasion dysphasia. In a survey of Penfield's cases of cortical excision for the relief of focal epilepsy, Roberts (1951) reports that aphasia followed operations on the right hemisphere only twice in 258 right-handed patients and three times in 23 left-handed patients. Unfortunately, no data as to the loci of the excisions or of the types of dysphasia are given. In the present paper a case is reported in which marked and relatively persistent dysphasia followed right temporal lobectomy. This case is of exceptional interest in so far as the patient was ostensibly right-handed. It thus represents a further addition to the sparse literature of "crossed aphasia" (Bramwell, 1899) in dextrals.

Case Report

Case No. 47010.—A labourer, aged 35, was admitted with a history of temporal lobe seizures of 16 years' duration. He first developed attacks in 1937, shortly after an illness consisting of acute right otitis media, acute right mastoiditis, and signs and symptoms of a cerebral abscess, which led to a negative exploration of the right sphenoido-temporal lobe. Early in 1949 the right mastoid was re-explored and later in the same year a radical mastoidectomy performed. Since this last operation the patient's attacks had become rather more frequent and on some occasions involved loss of consciousness. On neurological examination, there were no abnormal physical signs and an air-encephalogram was negative. The E.E.G. findings were reported as compatible with scarring from past inflammation involving the anterior portion of the inferior surface of the right temporal lobe. In view of the normal air-encephalogram, the patient was discharged on anti-convulsant medication.

He was readmitted nine months later on account of persistent generalized epileptic attacks, impairment of recent memory, and deterioration in personality. He had become slovenly in his dress, dirty in his habits, and liable to violent outbursts of temper. There were some paranoid features. A "metrazol" E.E.G. showed a single consistent focus in the right anterior temporal region. On July 1, 1944, formal right temporal lobectomy was performed (Mr. Wylie McKissock). After operation, the patient was at first totally aphasic, but would make some attempt to answer questions in writing (only single words could be produced). Speech returned fairly rapidly over the next few days but considerable dysphasia, predominantly receptive, remained in evidence during the ensuing weeks. Unfortunately, the patient's psychiatric state underwent no significant improvement and he was discharged elsewhere five weeks after operation.

Psychological Examinations.—On examination nine months before operation the patient attained an I.Q. of 95 on the Wechsler-Bellevue full scale. Although no dysphasia was apparent in conversation, occasional difficulty in finding words was noticed during testing and there were signs of minimal verbal defect on language intelligence tests. On the other hand, reading, writing, and calculation were not impaired. Re-examination two weeks before operation revealed no significant change in intellectual or linguistic attainment.

On examination two weeks post-operatively the patient's speech was markedly dysphasic. Although individual words were articulated normally, speech as a whole was marked by grave expressive defects. These comprised limited and inadequate formulation ("verbal aphasia"), condensed expression ("telegram-style"), and alteration in the prosodic quality of speech ("dysprosody" of Monrad-Krohn, 1947). The patient's speech was staccato and somewhat explosive, with marked disorder of modulation and "speech melody".

But little or no paraphasia appeared in spoken speech and naming objects was in general good. The patient could write his name and address without hesitation and readily copy a printed text. But writing either spontaneously or to dictation was much impaired, with omission of letters and frequent substitutions among the "small" parts of speech. For example: "To be or not to be. That is the question" was written as "Or not be not that as a qestion". On the receptive side the patient showed a marked defect in comprehension. Although ordinary conversation appeared to be fairly well understood, simple requests, e.g., selecting an object to oral command, were seldom carried out correctly and the patient's responses showed marked perseveration of the type described by Pick and Thiele (1931) in temporal lobe aphasia. Complicated requests were never understood. The patient was unable to understand the request to repeat words after the examiner and his immediate verbal memory could not

therefore be tested. He was, however, able to read aloud without gross error and to explain newspaper headlines more or less correctly. His interpretation of pictures, on the other hand, was excessively poor.

On re-examination three weeks post-operatively, speech showed some further improvement and the patient could now express his ideas at a simple level and conduct a conversation. His utterance, however, remained staccato and lacking in proper rhythm and stress. Comprehension, too, had very slightly improved and the patient was now able to repeat digits and short phrases to oral request. On the other hand, he still made many mistakes in carrying out instructions, even when these were quite simple and straightforward. Recognition of objects by sound (keys, matches) was intact. The patient could count coins scattered on the table and give the correct total in shillings and pence ; he could not, however, do the simplest calculation in his head. In writing, literal mistakes were still present but phrases could now be taken down to dictation without gross error. Reading aloud was adequate but the patient's grasp of the sense of what he read appeared somewhat defective. Drawing of objects from memory was excessively poor. On formal tests, the patient showed no deterioration on Kohs' block designs compared with the pre-operative level but performed very poorly on the picture-arrangement sub-test of the Wechsler-Bellevue scale. His performance in the Weigl sorting test was concrete, perseverative, and obviously much impaired.

The patient was re-examined 19 weeks post-operatively (by kind permission of the Physician Superintendent, Springfield Hospital). His oral speech was now found to be fluent but an occasional paraphasic error was recorded. Modulation and " speech melody " had also improved and no mistakes were made on object-naming tests. On the other hand, comprehension of speech remained markedly defective. Thus, when asked to undo the second button of his jacket, the patient undid all his buttons and then proceeded to do them up again. Very simple mental arithmetic could now be undertaken but the patient was unable to follow the simplest arithmetical reasoning test, whether given orally or in writing. Reading aloud was somewhat jerky and there were occasional paraphasic slips, but the patient appeared to grasp the sense of what he read. Writing to dictation still produced an occasional literal error. On intellectual testing, the patient's performance remained at much the same level as before : performance on the Weigl test was still impaired and his explanations of proverbs remained grossly defective. The patient was garrulous, discursive, and totally without insight ; his psychiatric condition remained unimproved.

Handedness in this case was of exceptional interest. The patient had always regarded himself as right-handed and was observed to favour his right hand in all ordinary unimanual activities. He denied strongly that he had been left-handed as a child or had ever wanted to write with the left hand. At the same time, he claimed considerable facility in the use of either hand and stated that he could use a hammer or saw, or throw a ball, left-handed. Attempts to write with the left hand, however, produced results no better than those commonly obtained from fully right-handed individuals. The patient appeared to have no definite foot-preference. His eye-dominance could not be satisfactorily tested on account of dysphasia.

Inquiry revealed that both parents had been right-handed. Of his seven siblings, one sister was left-handed (apart from writing), left-footed but right eye-dominant. Her husband and five children were, however, right-handed. The remaining six siblings were fully right-handed, as were also the patient's wife and their five children.

Discussion

The unusual feature in this case is the incidence of a severe post-operative dysphasia in an ostensibly right-handed man. Although expressive speech recovered rapidly and almost completely, the severe and persistent receptive disability (" word-deafness ") strongly suggests that the major hemisphere—or at any rate the major temporal lobe—was on the right side. This inference is supported by the fact that the patient was himself partly ambidextrous and that one of his sisters was fully left-handed. There is thus good evidence of definite—if relatively weak—sinistral characteristics, both familial and personal. Indeed the possibility that the patient was himself a " shifted sinistral ", i.e., a congenitally left-handed man converted by early training to the use of the right hand, cannot be wholly excluded, though no evidence to this effect was forthcoming. In our view, it is more plausible to suppose that the patient showed weak inborn specialization of hand-preference, i.e., that his ambilaterality was constitutional rather than acquired by training. If this view be correct, the patient is to be classified not as a " shifted sinistral " but as a congenitally, if weakly, right-handed man.

This interpretation gains a measure of support from certain cases of broadly similar type previously reported in the literature. Excluding certain very early case reports, we have been able to trace references to 15 cases in which aphasia has been found in association with right-sided lesions in right-handed patients. The main features presented by these cases are summarized in the Table. It will be seen that some degree of ambidexterity was present in three of the cases and a familial sinistral tendency in nine. Indeed there are only two really well authenticated cases (Mendel, 1914 ; Marinesco, Grigoresco, and Axente, 1938) in which neither personal nor familial indications of left-handedness could be established. It would therefore seem justifiable to anticipate some sinistral tendency in a case such as ours. At the same time it is important to bear in mind that not every case of aphasia in

TABLE

ANALYSIS OF 15 CASES FROM THE LITERATURE

Case	Handedness		Lesion	Verification	Physical Signs	Speech Disorder
	Personal	Familial				
Souques (1910)	Right	Not stated	R. vascular	—	Left hemiplegia	Mixed aphasia : severe, persistent
Mendel (1914)	Right	Right	R. embolism	Necropsy	Left hemiparesis	Motor aphasia : persistent
Kennedy (1916, Case 4)	Right	Both parents left	R. Rolandic gumma	—	Left-sided focal seizures, post-ictal left hemiplegia	Post-ictal aphasia after each attack
Kennedy (1916, Case 5)	Right	Two brothers left	R. subcortical glioma	Operation	Mild left hemiplegia	Post-operative aphasia : duration 10 days
Kennedy (1916, Case 6)	Right	Mother, brother, daughter left	R. cerebral haemorrhage	—	Left hemiplegia	Mixed aphasia : severe
Claude and Schaeffer (1921)	Right	Right	R. cerebral haemorrhage	—	Left-hemiparesis ; left-sided sensory loss	Motor aphasia : rapid but incomplete restitution ; dysgraphia, dyscalculia
Rothschild (1931, Case 1)	Right	Parents right; 2 (of 8) siblings left	R. embolism	—	?	Receptive dysphasia : transient
Rothschild (1931, Case 2)	Right	One son left	R. cerebral haemorrhage	—	?	Motor aphasia
Stone (1934) ..	Right	Parents believed right	R. temporal tumour	Necropsy	Left quadrantic field defect	Receptive dysphasia, dyslexia, dysgraphia, dyscalculia
Weisenburg and McBride (1935, Case 10)	Right, partly ambidextrous	Some left-handedness in family ; one child left-handed	R. middle cerebral thrombosis	—	Left hemiplegia; left-sided sensory loss	Expressive dysphasia : severe, persistent
Weisenburg and McBride (1935, Case 26)	Right	Not stated	R. middle cerebral thrombosis	—	Left hemiplegia; left-sided sensory loss	Expressive dysphasia : moderate, persistent
Chesher (1936, Case 9)	Right, virtually ambidextrous	One sister, one son left	R. cerebral tumour	Operation	?	Aphasia
Marinesco and others (1938)	Right	Right	R. vascular	Necropsy	Left hemiplegia	Mixed dysphasia : persistent
Subirana (1952, Case 9)	Right	One brother, one son left	R. vascular	R. temporal E.E.G.focus	Left hemiplegia	Dysphasia : transient
Whitty (1954, unpublished)	Right, partially ambidextrous	Mother and one sister left	? R. embolism	—	Left hemiplegia	Dysphasia : transient

a left-handed patient is due to involvement of the right hemisphere. Indeed, there are a number of well authenticated cases on record in which a left-handed patient, with sinistral familial antecedents, has developed aphasia from a lesion in the left hemisphere (Tilney, 1936 ; Cole, 1936 ; Goodglass and Quadfasel, 1954). All that can be said with confidence is that if an ostensibly right-handed patient develops aphasia from a lesion in the right hemisphere, it is likely that inquiry will reveal some measure of ambilaterality in the patient and/or sinistrality in the family pedigree.

It has been reported by Penfield and his associates (Roberts, 1951 ; Penfield and Jasper, 1954) that no systematic difference can be ascertained in the kinds of aphasia produced by excision of different areas of the brain. From this it has been concluded that the classical types of aphasia consequent upon injury or disease of particular cortical areas are not duplicated by surgical excision of the areas in question. In view of this somewhat surprising finding, it is perhaps worth calling attention to the fact that the picture in the present case, more especially after remission of the expressive speech defect, was altogether comparable to that typically observed in cases of injury or disease involving the major temporal lobe. Indeed, the patient, in the later post-operative stages at least, may be said to have presented a classical " word-deafness " of moderate severity. The only atypical feature was perhaps the comparative lack of paraphasia and jargon, which do not, however, necessarily accompany receptive dysphasia. Although it may be argued that the patient's psychiatric disorder, which was unimproved by operation, indicates a cerebral dysfunction not limited to the temporal area, it is none the less of interest to note that a true receptive dysphasia, not present before operation, was in this case found to follow surgical excision of the (presumably major) temporal lobe.

The possibility still remains that speech was bilaterally represented in the case under discussion. This issue has been abundantly explored in the recent literature (Conrad, 1949 ; Subirana, 1952 ; Humphrey and Zangwill, 1952) and has been given systematic theoretical expression by Goodglass and Quadfasel (1954) in a valuable paper. Although it is a possibility which certainly cannot be ruled out, it must be borne in mind that many cases of unilateral lesion involving the language zones of one or other hemisphere have been reported in sinistrals without resulting dysphasia. Strictly

unilateral representation of speech must therefore occur in some sinistrals at least. Although Goodglass and Quadfasel (1954) have allowed for this contingency in their theory of "cerebral ambilaterality", it must be admitted that no certain evidence of bilateral speech representation as yet exists. Until such evidence is to hand, it is perhaps wiser to conclude that language in the case under discussion was represented in the right hemisphere, and that this anomaly of dominance is to be linked with a weak constitutional sinistral strain.

Summary

A case is reported in which right temporal lobectomy was performed for the relief of temporal lobe epilepsy and associated psychiatric disturbances. Although preferentially right-handed, the patient developed severe post-operative dysphasia, especially marked and persistent in the receptive sphere. The significance of the findings in relation to handedness, familial sinistrality, and cerebral dominance is briefly considered.

We wish to express our gratitude to Dr. E. A. Carmichael and Mr. Wylie McKissock for their kind permission to study and communicate this case.

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THE MAY (1955) ISSUE

The May (1955) issue contains the following papers :—

Studies in Traumatic Epilepsy, Part 3 : Visual Fits. W. Ritchie Russell and C. W. M. Whitty.

The Arterial Supply of the Spinal Cord and Its Significance. D. H. M. Woollam and J. W. Millen.

Encephalitis in Loa-Loa Filariasis. L. van Bogaert, A. Dubois, P. G. Janssens, J. Radermecker, G. Tverdy, and M. Wanson.

Observations on the Reaction Time to Cutaneous Thermal Stimuli. P. P. Lele and D. C. Sinclair.

Chronic Proliferative Osteitis of the Skull. J. E. M. Dutton and G. L. Alexander.

The Association of Dementia with Radiologically Demonstrated Cerebral Atrophy. R. H. Gosling.

Choroid Plexus Papilloma Causing Spontaneous Subarachnoid Haemorrhage. J. Ernsting.

The Use of Dehydroisoandrosterone in Psychiatric Practice. E. B. Strauss and W. A. H. Stevenson.

Ischaemic Sensory Loss in Patients with Spinal and Cerebral Lesions. R. W. Gilliatt.

Anxiety and an Autonomic Reaction to Pain. Malcolm Piercy, Alick Elithorn, R. T. C. Pratt, and Margaret Crosskey.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 12s. 6d.

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IMPAIRED IDENTIFICATION OF FACES AND PLACES WITH AGNOSIA FOR COLOURS

REPORT OF A CASE DUE TO CEREBRAL EMBOLISM

BY

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Wheresoe'er I turn my view
All is strange, yet nothing new . . .
SAMUEL JOHNSON

Visual agnosia usually develops in a context of diffuse or progressive cerebral disease. The disorder is often difficult to analyse because of associated dysphasic disturbances, visual field defects, drowsiness or impaired attention, poor memory, inadequate insight, or " mental confusion ". In other instances the difficulties are due to a low initial intelligence, to undue suggestibility, or to an abnormal emotional reaction. Symptoms of agnosia in patients with raised intracranial pressure or diffuse cerebral arteriosclerosis are notoriously difficult to evaluate.

It must be very rare indeed for agnosia to develop acutely and to constitute the sole disability in a person of high intelligence and good personality. I have recently had the opportunity of observing one such patient in whom cerebral embolism was the basis of a " visual agnosia ", strikingly selective in its manifestations. The case is described here in some detail as it probably has important neurological implications concerning the status of prosopagnosia (agnosia for faces) and its relation to achromatopsia (colour agnosia), and to a peculiar, and I believe hitherto unrecorded, disorder of spatial thought.

Critchley (1953) in a recent discussion on " parietal " symptomatology has emphasized the inadequacy of many case reports and the difficulties involved in deciding whether the failure to mention certain complex phenomena should imply that they were in fact absent, or merely that they were not specifically sought for. In a case such as the one about to be described fairly detailed comment as to the absence of certain signs and symptoms is therefore not only permissible but proper.

In the following case report the patient's own words are quoted wherever possible. He wrote a full account of his experience from which certain passages are here excerpted.

Case Report

A. H., aged 51, a mining engineer and colliery manager, was admitted to the Neurological Department, Cardiff Royal Infirmary, on January 4, 1954. He had suffered from chorea in childhood. In 1948 mitral stenosis was diagnosed. In 1952 he developed auricular fibrillation and slight congestive failure and spent five weeks in hospital. He responded well to treatment and returned to work. There had been no embolic episodes that he was aware of.

On the evening of June 10, 1953, he suddenly felt unwell after a couple of drinks at his club. He called out for help but remembered nothing of the events of the subsequent 12 hours. He did not lose consciousness. He appeared confused, was taken home by car, and had to be helped to bed. He spent a restless night, complaining of headache, but did not vomit.

" At about 8 o'clock next morning I got out of my bed. My mind was clear but I could not recognize the bedroom. I went to the toilet. I had difficulty in finding my way and recognizing the place. Turning round to go back to bed I found I couldn't recognize the room, which was a strange place to me . . ."

" I could not see colour, only being able to distinguish light objects from dark ones. Then I found out all faces were alike. I couldn't tell the difference between my wife and my daughters. Later I had to wait for my wife or mother to speak before recognizing them. My mother is 80 years old."

On the first morning he had complained of heaviness of the left hand and of a " stinging " feeling in the left index finger and about the angle of the mouth, on the left side. Both these symptoms cleared within a few days. At no time was there any difficulty in the utterance or comprehension of speech. His subsequent behaviour was normal, although he became more reticent than usual. He showed no evidence of apraxia and could shave, dress himself, do up his shoe laces, and make his bed. Within a few days his only residual symptoms pertained to vision and to the interpretation of things seen.

He became almost immediately aware of an altitudinal scotoma in each eye. " Below, I can see detail quite clearly. Then there is a narrow blotch of darkness across the middle of whatever I look at. It has a straight

lower edge but on top and at the sides the border is less sharp. Whether I shut one eye or the other, things look much the same. I have learned to look above the blotch to pick out any details originally missed."

Colour perception was totally lost. " Everything appears in various shades of grey. My shirts all look dirty and I can't tell one of them from the other. I have no idea which tie to wear." " I can't tell whether the light in a room is on or off and from a distance I don't know whether the fire is burning or not." " I have difficulty in recognizing certain kinds of food on my plate, until I have tasted or smelled them. I can tell peas or bananas by their size and shape. An omelette, however, looks like a piece of meat and when I open a jar I never know if I'll find jam or pickles in it ! " He readily recognized individual items of cutlery, glassware, furniture, garden tools, or other objects in everyday use, " provided colour isn't the main clue as to what it is ".

The patient analysed his difficulty in identifying faces with considerable insight. " I can see the eyes, nose, and mouth quite clearly but they just don't add up. They all seem chalked in, like on a blackboard. I have to tell by the clothes or voice whether it is a man or woman, as the faces are all neutral, a dirty grey colour. The hair may help a lot, or if there is a moustache." " All the men appear unshaved." " I cannot recognize people in photographs, not even myself. At the club I saw someone strange staring at me and asked the steward who it was. You'll laugh at me. I'd been looking at myself in a mirror." " I later went to London and visited several cinemas and theatres. I couldn't make head or tail of the plots. I never knew who was who." " I bought some copies of *Men Only* and *London Opinion*. I couldn't enjoy the usual pictures. I could work out what was what by accessory details, but it's no fun that way. You've got to take it in at a glance."

He had some difficulty with animal faces also. "They are easier to recognize than human faces, because the rest of an animal varies so much more than does the rest of a man. In real life I could tell a cat from a dog, or a horse from a cow, but it would be more difficult from pictures, especially if only the face is shown."

He had no difficulty in revisualization. " I can shut my eyes and can well remember what my wife looked like or the kids." He described his dreams as " not frequent, but just as vivid as before ". He therefore showed none of the features of what Nielsen (1946) called " irreminiscence ", the syndrome described by Charcot (1883) and Wilbrand (1887) and characterized by a failure to conjure up visual images and by a loss of the visual components of dreaming.

He complained a lot of his inability to recognize places. There was no loss of topographical memory. " In my mind's eye I know exactly where places are, what they look like. I can visualize T . . . Square without difficulty, and the streets that come into it." " I know the order of the shops." " I can draw you a plan of the roads from Cardiff to the Rhondda Valley." " It's when I'm out that the trouble starts. My reason tells me I must be in a certain place and yet I don't recognize it. It all has to be worked out each time. For instance, one night, having taken the wrong turning, I was going to call for my drink at the Post Office. I got back to the main street and took my usual turn again." Or even more strikingly : " My difficulty with buses is to know where to get off. Two colleagues of mine once got on at the same stop. One of them was a totally blind man. I told them I wanted to get off at P . . . Square. The blind man offered to put me down there, which he did without trouble."

He seemed to have difficulty in assimilating new topographical data. " It's not only the places I knew before all this happened that I can't remember. Take me to a new place now and tomorrow I couldn't get there myself."

He stated that during the first weeks of his illness there had been some difficulty in reading, but that this had rapidly cleared up. He was an observant witness and there were no residual dyslexic difficulties. He did not think his calculating ability had been affected. There had been no " body-image " disorders.

He was questioned closely as to whether he thought his sense data for visual synthesis were adequate. His engineering training made it easy for him to grasp the issue at stake : he did not consider his " raw materials " defective. He was emphatic that the scotomata, "although a nuisance were not what really mattered", and he made the very pertinent enquiry as to why, if they were of significance, they should prevent him from identifying faces but did not interfere with his perception of other objects. He admitted that the loss of colour vision contributed to his difficulties. He was occasionally " worried by the nearness of things " and gave an excellent description of the phenomenon of pelopsia : " the eyes have become telescopic. Things sometimes seem just on top of me, although not particularly large. Well known distances appear a third of what they ought to be." There was no other impairment of stereoscopic vision and the landscape had normal relief. He could assess without difficulty the relative propinquity of various objects, both in front of him and on either side. The dimensions of objects looked at were in no way distorted, there was no abnormal tilt to their edges and no blurring, discontinuity, or movement of their outline. There was no complaint of visual perseveration and no abnormal affective reaction to the objects in his monochromatic world. They appeared to him neither sinister nor endowed with particular charm, but—not unnaturally— " rather dull ".

Examination.—On examination on January 4, 1954, mitral stenosis and auricular fibrillation were found. The ventricular rate was 70 to 80 per minute. There was a minimal pulse deficit. Blood pressure was 130/90 mm. Hg. He was receiving " digoxin ". There was no evidence of congestion and no signs of bacterial endocarditis.

He was right-handed. On neurological examination the only abnormalities detected were in the visual fields (Fig. 1). Uncorrected acuity was 6/6 in each eye. The fundi were normal. On the perimeter there were narrow non-congruous homonymous sector defects in the left

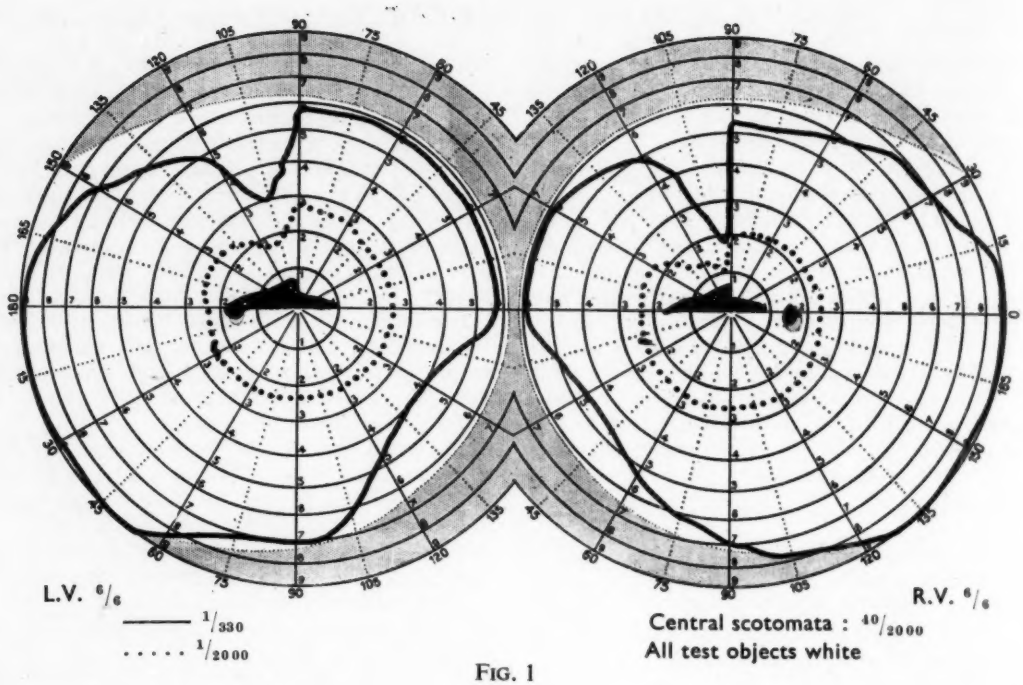

FIG. 1

upper quadrants, well shown by the 1/330 isopters. (The patient was unaware of these defects.) A central defect in each field was further explored on the screen. The patient was an excellent witness and gave consistent replies on repeated testing. A 40-mm. white object outlined a large "altitudinal" absolute scotoma in each field extending both sides of the vertical meridian. Each scotoma was limited inferiorly by the horizontal meridian, except where fusion with the blind spot had occurred. (In Fig. 1 these central defects are recorded on the same scale of coordinates as used for the 1/330 isopters. These "half-moon" shaped central defects are best considered as made up of two adjacent quadrantic scotomata, each with its apex at the fixation point.) A 50% reduction in illumination did not markedly alter the size of the defects. Confrontation tests revealed no visual inattention. He localized objects accurately in both right and left half-fields.

Stereognostic perception was excellent, even when wearing a pair of surgical rubber gloves. He localized stimuli accurately in the limbs and discriminated normally between single, double, and treble stimuli applied to various parts of the body. Graphaesthetic sense was not impaired. Detailed and repeated sensory testing failed to reveal—or to induce—any "cortical" type of sensory loss.

He was of above average intelligence and his general level of awareness was extremely keen. His memory was remarkable. He repeated the Babcock sentence correctly at the first attempt and his span of digit retention was eight forwards and six backwards. There was no hesitation in his speech and he could obey complex orders. He read smoothly and had no trouble in understanding and later describing what he had read. "Spontaneous" writing, and writing to dictation were orderly and he made no spelling mistakes. He promptly recognized, named, and demonstrated the use of a wide variety of test objects. He showed no difficulty in sorting out geometrical figures according to form and complicated patterns were promptly recognized. The significance of line drawings was immediately apparent to him and he could accurately describe the content of various pictures he was shown. He had no difficulty in identifying his own fingers or those of his examiner or any other part of their respective anatomies, including mouth, nose, eyes, and ears. There was no right-left confusion or acalculia. He could draw well: his daisies were most artistic and his bicycles showed a wealth of accurate technical detail. There was no neglect or imperception of any part of extrapersonal space. He could assemble a jig-saw puzzle and he showed no constructional apraxia in "match-mosaic" tests. He could play draughts and chess—but found playing cards too much effort.

He mixed readily with the other patients in the ward but rarely spoke unless spoken to first. He could not identify his medical attendants. "You must be a doctor because of the coat, but I don't know which one you are. I'll know if you speak." He failed to identify his wife during visiting hours. She was told one day, without his possible knowledge, to walk right past his bed but he did not show the least sign of recognition. Repeated attempts were made to "catch him out" but none succeeded. If the disability was a feigned one, it was a performance of quite unbelievable virtuosity and consistency. He made repeated journeys to various parts of the hospital and got lost on several occasions. He once walked into a female ward by mistake. Neither its disposition nor its occupants struck him as any different from those of the ward he had just left.

The "prosopagnosia" was specifically investigated. He failed to identify pictures of Mr. Churchill, Mr.

Aneurin Bevan, Hitler, Stalin, Miss Marilyn Monroe, or Mr. Groucho Marx. When confronted with such portraits he would proceed deductively, analysing one feature after another, searching hard for the " critical detail " which would yield the answer. In human faces, this was rarely forthcoming. There was somewhat less difficulty with animal faces. A goat was eventually recognized by its ears and beard, a giraffe by its neck, a crocodile by its dentition, and a cat by its whiskers.* With none of these animals could he immediately grasp the meaning of the face. He took five to 10 seconds over each picture. The face of a monkey lacked " critical detail " and was not identified.

Investigations.—Radiographs of the skull showed no abnormality. The Wassermann and Kahn tests were negative in the blood. The cerebrospinal fluid was normal in pressure and composition. The electroencephalogram was normal. Vertebral angiography (Dr. Arthur M. Jones) showed defective filling of the right posterior cerebral artery, the right vertebral artery having been punctured. The other branches of the basilar artery and the left posterior cerebral artery (and its terminal branches) were well outlined.

Discussion

The main features of this most unusual case may be summarized as (1) achromatopsia (colour agnosia); (2) a disorder preventing the identification of faces; (3) a peculiar disorder of spatial thought which rendered the patient incapable of identifying places (but without impairment of topographical memory, spatial imperception or neglect, or difficulty in recognizing landmarks); (4) an almost complete absence of other " parietal " signs or symptoms; (5) scotometric evidence of small bilateral occipital lesions.

The Achromatopsia.—Achromatopsia denotes an inability to perceive colour distributed throughout the whole of both visual fields. Any abnormality confined to part of the field is more akin to disorder of the visual analysers than to the " higher level " disturbances considered here. Achromatopsia of cerebral origin may occur without visual field defect although Critchley (1953) considers it " doubtful whether colour sense can be altered . . . without some corresponding disturbance in the appreciation of form ". Whether achromatopsia ever develops in the absence of other defects of gnosis is still the subject of controversy. Nielsen (1941) maintains that small cerebral lesions may affect selectively the recognition of certain attributes of objects in general (such as colour, form, dimension, and movement) and, to some extent, the case here reported supports this contention.

It is not yet known whether achromatopsia has any localizing or even lateralizing significance. Critchley (1953) believes that it may occur with unilateral cerebral disease, and that the lesion is then usually in the dominant hemisphere. The patient A. H. had bilateral infarcts but the size and shape of the field defects show that the main lesion was right-sided. The only unequivocal evidence of disease in the left hemisphere was provided by those small parts of the scotomata in each field situated to the right of the vertical meridian. The left-sided lesion was situated very far back, in the infracalcarine striate cortex. If this small lesion is of no significance in causing achromatopsia it must be conceded (1) either that the symptom may arise from disease affecting the subordinate right hemisphere (of which there was evidence in the shape of the initial left-sided paresis and facio-brachial paraesthesiae and of the sector defects in the left upper quadrants) or, (2) that achromatopsia may be virtually the only reflexion of a dominant hemisphere lesion, or, finally (3) that bilateral disease is necessary for achromatopsia to develop and that the left-sided lesion may be clinically silent.

It is difficult to know what role to attribute to small occipital infarcts revealed by scotometry. Spalding (1952) has carefully studied the effects of penetrating injuries to the striate cortex and many of the recorded visual fields in his excellent study showed small quadrantic scotomata, with their apices at the fixation-point, very similar to those of patient A. H. Total achromatopsia was not encountered with these partial lesions (personal communication).

This case illustrates how achromatopsia may arise on the basis of localized brain disease, causing few other symptoms or signs. It does not help, however, in the vexed question of whether such disease needs to be bilateral, or, if the symptoms can arise from unilateral disease, which hemisphere is the most likely to be responsible.

The Prosopagnosia.—It is not well established whether considerations of cerebral dominance are of the same importance in the recognition of general visual data as they are in the recognition of symbols (such as letters and numbers). Lesions of the dominant parietal cortex (Brodmann area 39) or of its afferent fibres from the striate cortex affect the recognition of written symbols and the results of such lesions are but poorly " compensated ". With lesions of the shorter pathways between the striate cortex (area 17) and adjacent occipital area 18 (or with lesions of area 18 itself) it is the recognition of other (non-symbolic) visual data that is affected, and here experience shows that considerable improvement follows unilateral lesions in the dominant

*In these respects he showed a striking resemblance to Bodamer's Case 2 (*vide infra*) who eventually recognized a portrait of Hitler by the *Bard und Scheitel* (moustache and parting).

occipital lobe. Current opinion, therefore, has it that bilateral lesions are necessary for permanent symptoms of visual agnosia to develop.

Critchley (1953) states that " visual agnosia . . . must be admitted as a rarity in clinical practice ". He enumerates a number of points which may throw doubt on whether a patient's disability is in fact a visual agnosia : quantitative and qualitative visual defects, the absence of visual imagery, the presence of dysphasia or other gnosic or praxic difficulties, general mental confusion, and the absence of insight into the disability (anosognosia). Many of the classical recorded cases of visual agnosia showed these associated features in varying degree, and their interpretation is hence very difficult. There were few such complicating factors in the patient here described.

The " agnosia " in this patient was highly differentiated in its manifestations. Opinion is divided on whether such specific forms of visual agnosia do in fact occur. Nielsen (1941) distinguished between agnosia for animate and agnosia for inanimate objects which he relates to lesions of the upper and lower parts of Brodmann's area 18 respectively. Teitelbaum (1943) analysed agnosia into numerous variants. To Critchley (1953), however, " pure cases of partial and specific visual agnosia suggest both an incompleteness of the clinical study and an ignorance of the intricate modifications of the patient's total behaviour ".

In most case reports of prosopagnosia the symptom is only a facet of a more widespread disturbance (Müller, 1892 ; Goldstein and Gelb, 1918 ; Heidenhain, 1927). Hoff and Pötzl (1937) recorded its occurrence in almost isolated form, but in a patient also suffering from loss of visual memory. More recently Bodamer (1947) propounded an elaborate psychological theory to account for his observations in two patients in whom prosopagnosia was the outstanding feature. Both had sustained, among others, bilateral occipital injuries. Neither of these cases had experienced difficulty in revisualizing long-familiar faces. (Bodamer's third patient differed in several respects and was probably suffering from a metamorphopsia confined to faces, without prosopagnosia.) It is of considerable interest that colour vision was affected in both Bodamer's cases and in all the cases mentioned above. Cases of prosopagnosia have, however, been described in which colour vision was not affected (Jossmann, 1929).

According to Bodamer (1947) the human face is in a perceptual category of its own. Other forms of agnosia are not necessarily associated with prosopagnosia (the dissolution of the special function of identifying faces). In prosopagnosia, the patient, although still able to recognize the separate components of a face, is no longer capable of the synthesis permitting identification of the physiognomy as a whole. The defect was considered a manifestation, confined to the face, of what Wolpert (1930) had termed " *Simultanagnosie* ". There was a defect in the " simultaneous " awareness of the perceptual data underlying physiognomy. Bodamer rejects the idea that this was due to the field defects shown by both his patients.

Bodamer went further, however. An eye-area, or " ocula ", as he called it, had been " spared " in both his patients. Reference to the work of certain child psychologists suggested that, ontogenetically, this eye-area was of considerable importance. Bodamer considered his patients with prosopagnosia to have reverted to an infantile phase of perception. Apart from the eye area they perceived but little of the faces of those about them, which appeared blurred.

Whatever one's views about Bodamer's theories, his detailed case reports, together with a few others, offer some clinical evidence for the concept of an unusual, and perhaps specific, disorder in the " visuognosic " sphere concerning the identification of faces. The precise scotometric data in the present case may be of relevance. The total data suggest that the disturbance may arise as a result of bilateral occipital lesions, but there are too few case reports with detailed visual field studies or necropsy confirmation for one to have any certainty about the localizing value of the symptom.

Comment seems called for as to the propriety of the term " prosopagnosia " to denote an inability to identify faces. Patients with this disability are rarely in any doubt as to the fact that it is faces that are situated above the necks of those about them. Modern art may depict a variety of objects at this site but it is doubtful if such apparitions are ever part of the experiential world of patients with parieto-occipital disease. Individual facial features, however distorted they may appear from metamorphopsia, are usually perceived for what they are (an eye, a nose, a mouth) and their geometric relationship is usually preserved. There is clearly more to a face than the sum of its structural components. Colour is probably not of fundamental importance. A portrait in black and white is recognized as easily as a portrait in colour.

It is suggested that the fundamental defect, in this case and perhaps in others, was not in the visual sphere. Neither was it agnosia in the ordinary sense. Faces were recognized as faces, they were not identified as particular faces. There was there-

fore difficulty in appreciating the full significance of what had been seen and recognized and there followed an inability to fit such data into the pattern of previous experience. Faces failed to elicit the engrams forming the basis of memory although memory itself was not impaired and there was no difficulty in " re-visualization ". The disturbance was probably at a higher level than gnosis.

The Disorder of Spatial Thought.—The patient's inability to recognize places was a most unusual disturbance of spatial thought. His topographical memory was good, as could be inferred from his accurate descriptions of paths, roads, the layout of the mine-shafts, and from his excellent performance in drawing maps of places familiar to him before his illness. There was no evidence of neglect or imperception of any part of extra-personal space, localization of objects in space was excellent, and he showed no difficulty in inter-dimensional spatial manipulations. There was no loss of stereoscopic vision (Riddoch, 1917 ; Holmes and Horrax, 1919) and no visual allo-aesthesia (Herrmann and Pötzl, 1928).

Orientation in abstract space, known to him before his illness, was normal. For instance, he could outline, on plan of Cardiff, the appropriate route for getting from the hospital to the railway station or football stadium. Yet when confronted with the concrete task of so doing his performance was poor. He would have difficulty in reconciling the reality about him with the plan in his mind in convincing himself that he was in a given situation. " I have to keep the idea of the route in my head the whole time, and count the turnings, as if I were following instructions that had been memorized." " The places are all strange, yet common sense tells me they are not new to me."

At a purely conceptual level there did not appear to be anything unusual in his ideas about space. Critchley (1953) has stressed the variability of such ideas in normal people. " The conceptions of space held by a philosopher, a mathematician, and an artist are probably very different one from the other—and all of them are quite unlike the naïve ideas of the ordinary layman." A. H.'s ideas of space were doubtless those of a graduate of the University of Wales with a B.Sc. degree in engineering and with little, if any, inclination for metaphysical speculation. He was a perfectly normal person in all these respects.

It is suggested that his difficulties in spatial orientation were of a type not hitherto well recognized and derived from an inability to assimilate environmental experience completely. His environment lacked perhaps some subtle attribute which one might call topographical significance. I do not wish to imply that he was unaware of the nature of houses or streets. He could at a glance tell terraced council-houses from detached villas, a living room from an office, a country lane from a main road. There was therefore no agnosia for landmarks. Such objects, however, normally elicit more than a formal recognition. They are not merely " houses " or " roads ", they are particular houses, houses-in-a-certain-position, particular roads, roads-going-from-A-to-B ; they have, in fact, a specific and topographical as well as an abstract and generic significance.

It is suggested that, devoid of this attribute of topographical significance, the patient's surroundings failed to elicit the appropriate topographical memories. Identification of a particular environment was therefore defective although there was no misinterpretation of the nature of its individual components. The similarity between this presumed disorder and his difficulty in identifying faces is apparent. In neither instance was the disturbance primarily one of the visual analysers nor was it agnosia as usually understood. Identification failed, in the presence of perceptual data adequate for gnosis, in the ordinary sense. (It is probably no coincidence that a defect of identification, as distinct from recognition, should, in everyday life, manifest itself in precisely such perceptual categories as faces and places.)

A defect such as the one envisaged would account for (1) his persistent difficulty in identifying previously well known places or faces, and (2) his inability to remember new places or faces. We have all experienced the peculiar sensation felt on visiting a strange town for the first time. Although at first devoid of topographical significance for the observer, the new buildings and streets, the " feel of the place " rapidly acquire meaning. At a subsequent visit the impression is a very different one. When meeting people for the first time something similar occurs. They cease to be people and become persons. The patient was perhaps incapable of this adjustment. New surroundings or faces, seen for the first time after his illness, retained indefinitely their quality of newness. Perhaps they could not be incorporated as memory because, to the patient, they were lacking in some essential attribute. Previously known places and faces, again lacking this attribute, failed to elicit remembrance. Memory is, after all, an aggregate of sensory experiences, each occurring within certain patterns of circumstance, each engendering certain affective reactions (often beyond the realm of consciousness), and each definitely

related to certain coordinates of time and space. Devoid of this garb, who knows how easily new experience could be registered, or previous experience recalled?

Other Possible Interpretations.—This case offers no real support for the *Gestalt* theory of visual agnosia propounded by Goldstein and Gelb (1918). With regard to such special object-categories as places and faces there was, it is true, a discrepancy between the recognition of parts and the identification of the whole, but the tests resorted to revealed no abnormality in the formation of primitive visual *Gestalten*. There were no persistent dyslexic difficulties, and all geometrical figures were readily recognized without recourse to the tracing movements of head or hand exhibited by Goldstein and Gelb's famous patient Schn. It is, moreover, difficult to conceive of a disorder of *Gestalt* formation so highly specific in its manifestation.

Could the patient's disability be explained on the basis of other defects of what Lissauer (1889) called "apperception"? Much modern work stresses the importance of subtle functional disturbances in the visual analysers in causing symptoms usually attributed to agnosia. Bay (1953), for instance, doubts there is any such clinical entity as visual agnosia and holds that what is usually so denoted is in fact a primary sensory defect complicated by a variable degree of dementia. As he graphically puts it, "sensory defect and mental deterioration increase and multiply each other". The new techniques for testing perception in various parts of the visual field (tachistoscopy, local adaptation-time, rate of flicker-fusion) will often show the "effective field" to be of smaller dimensions than the field determined by perimetry or scotometry under standard (optimum) conditions. In Bay's view prosopagnosia results in most cases from contraction of the effective field to less than 5°. Such a field precludes a simultaneous survey of the face, and hence will prevent the patient from obtaining a "*Gestalt* of the physiognomy". A similar interpretation is offered by Bay for the disorders of spatial orientation not infrequently accompanying prosopagnosia and relating to environments first encountered after the onset of the disorder.

In relation to these claims it may be pointed out that the patient here described had a visual acuity of 6/6 in each eye (despite his scotomata), that metamorphopsia was minimal (occasional pelopsia only), and that there was no hint of dementia. Special tests to assess local adaptation-time and the rate of flicker-fusion have not been performed to date, neither has tachistoscopy. It seems, however, improbable that any abnormalities revealed by these techniques would have resulted in an effective field of less than 5°, in view of the position of the 1/330 and 1/2000 isopters determined by standard methods. It is, moreover, rather improbable that any such qualitative defect in the field would have resulted in so highly specific a disability.

Summary

A patient with mitral stenosis and auricular fibrillation developed, as a result of cerebral embolism, achromatopsia (colour agnosia) and an inability to identify faces and places. There was no loss of topographical memory and no difficulty in revisualizing faces.

Scotometric studies suggested small infarctions in each infracalcarine striate cortex.

The symptoms are analysed with special reference to their relation to (*a*) agnosia and (*b*) to the defects in the visual fields. The difficulties involved in attributing to them any precise localizing significance are mentioned.

The concept of prosopagnosia is discussed and its possible relation to a peculiar, and hitherto unrecorded, disorder of spatial thought is pointed out.

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RAUWOLFIA SERPENTINA (SERPASIL) IN PSYCHIATRY

BY

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The therapeutic problem of satisfactorily controlling acute and chronic states of psychomotor excitement is an ever-present one confronting psychiatrists engaged in hospital practice. Admittedly, the application of current methods of treatment, such as systematic pharmacological sedation by means of barbiturates and other drugs or electroconvulsive therapy, will in most cases control excited behaviour. It is a common experience, however, that even after adequate and efficient treatment a number of patients either do not respond satisfactorily to these measures or exhibit a tendency to relapse fairly rapidly. *Rauwolfia serpentina* (" serpasil "), a new drug, is of undoubted value in the treatment of these cases and may in time supersede the established methods, which are not altogether free from disadvantages and risks, however much minimized by skilled and efficient application.

Pharmacology

Reserpine (" serpasil ") is the chief active principle of *Rauwolfia serpentina*. It is a crystalline alkaloid isolated from a plant, *Rauwolfia serpentina*, growing mainly in India but also found in Ceylon, Burma, the Malay Peninsula, and in certain islands of that area. It is a rather small plant, growing to a height of about 3 ft., and bearing white or pinkish flowers. It has long, tapering, crooked roots, which contain most of the alkaloid.

This drug has long been used in India, principally by Ayurvedic practitioners as a remedy for snake bites and as a cure for dysentery. Latterly, it was used for insomnia, hypochondria, and insanity. Its use in Europe was known over 300 years ago, when it was stated to be of value in the treatment of anxiety states. The empirical formula of *Rauwolfia serpentina* is $C_{33}H_{40}O_9N_2$, and the structural formula proved to be as shown (Siddiqui and Siddiqui, 1931 ; Müller, Schlittler, and Bein, 1952 ; Dorfman, Furlenmeier, Huebner, Lucas, MacPhillamy, Müller, Schlittler, Schwyzer, and St. André, 1954).

The principal action of the drug appears to be an alteration of sympathetic-parasympathetic balance by the partial suppression of sympathetic predominance at the hypothalamic level (Plummer, Barrett, Wagle, and Yonkman, 1953 ; Trapold, Plummer, and Yonkman, 1954 ; Tripod, Bein, and Meier, 1954.)

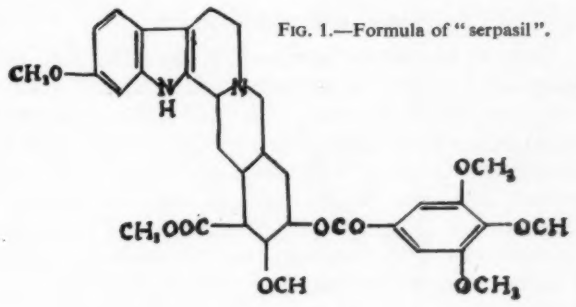

FIG. 1.—Formula of " serpasil ".

Physiological Effects

Serpasil, administered in tolerable doses, causes sedation, bradycardia, hypotension, nasal stuffiness, and gain in weight. It can be taken indefinitely and does not result in the development of tolerance or addiction. Excessive dosage is stated to cause diarrhoea, nightmares, and agitated depression (Wilkins, 1952 ; Wilkins and Judson, 1953 ; Wilkins, Judson, and Stanton, 1952 ; Wilkins, Judson, Stone, Hollander, Huckabee, and Friedman, 1954).

None of the cases reported here required treatment for diarrhoea or nasal stuffiness. Some patients complained of tiredness and drowsiness, but proved capable when stimulated of immediately mobilizing sufficient energy to overcome their sleepiness and carry out required activity. A subjective sensation of dizziness was experienced by two patients at the beginning of medication. These symptoms proved transient, disappearing in a week or ten days, and in all cases the patient remained ambulant. The only other significant side-effect occasionally complained of was heavy dreaming, sometimes erotically tinged. Blood examinations and analysis of urine

remained normal throughout treatment and subsequently.

Psychological Effects

Perusal of the literature on *Rauwolfia serpentina* indicates that in the opinion of several investigators the drug produces certain definite psychological effects. Under its influence patients tend to be less susceptible to circumstances and situations formerly capable of producing symptoms such as anxiety or depression. They exhibit greater spontaneity, tend to be more sociable and optimistic, and as a result are more accessible to psychotherapy and in a better position to respond effectively. The sedative and relaxing effects of the drug appear to diminish tension and to exert a calming effect on excited, tense, hyperactive patients (Kline, 1954; Hakim, 1953).

Dosage and Administration

Serpasil is effective administered by either oral or parenteral routes. In cases exhibiting severe excitement parenteral injection of 5 mg. rapidly produces a calming effect. Depending on the severity of the excitement this can be repeated eight hourly, or the initial dose can be followed by oral medication, beginning with 1 mg. every four hours. Parenteral administration can usually be discontinued after one or two days, and the oral dosage may be increased to 5 to 15 mg. daily as required. No untoward side-effects were observed with these doses. Shivering and flushing of the entire body sometimes occurred 30 to 45 minutes after an intravenous or intramuscular injection of 5 mg. Occasionally a patient complained of vertigo or weakness but all remained ambulant. Administration of the drug was invariably accompanied by a drop in blood pressure and bradycardia. Correlation between the sedative effect and the effect on blood pressure and pulse rate was not established.

In less pronounced psychomotor restlessness, such as that seen in senile agitation, doses of from 0·5 mg. to 1 mg. t.i.d. are usually sufficient to produce tranquillity.

Experience gained in the use of the drug indicates that treatment can be continued indefinitely without any apparent ill-effects.

Concomitant administration of other drugs does not impair the effectiveness of " serpasil " (Kline, 1954). There is a reference in the literature to a death while a patient was receiving both digitalis and *Rauwolfia serpentina* (De and Chatterjee, 1941).

Hakim claimed good results in psychoses and psychoneuroses using a preparation containing *Rauwolfia serpentina* combined with E.C.T. (Hakim, 1953).

Results

One hundred and eighteen male patients ranging in age from 20 to 76 years treated with " serpasil " over a period of eight months have provided experience on which this report is based. The subjects for testing, with the exception of 12 cases of acute mania and two organic confusional states due to uraemia, were selected from chronic patients persistently exhibiting disturbed behaviour.

Serpasil proved to have a definite sedative action although it was not equally effective in all cases. The group of manic depressive patients in the manic or hypomanic state responded best. The tranquillizing effects of the drug became apparent within 24 hours of administration either by the parenteral or oral route, eliminating any necessity for barbiturate sedation or E.C.T. Psychomotor excitement diminished and was replaced by cooperative behaviour rendering nursing care and attention easier.

The drug given in adequate dosage appears to control satisfactorily most kinds of severe excitement commonly encountered in admission or refractory wards, e.g., catatonic schizophrenia, organic toxic confusional states as seen in uraemic conditions, post-epileptic confusional states, and senile psychoses.

Due to the beneficial influence of " serpasil " it was found practicable, in one refractory ward, to empty permanently all the side-rooms of patients who previously had occupied them for long periods.

The incidence of impulsive and noisy conduct was reduced following exhibition of the drug, an observation confirmed by the evidence of daily ward records and casualty reports.

TABLE
ANALYSIS OF RESULTS

Condition	Recovered	Much Improved	Improved	Unchanged	Total
Schizophrenia ..	—	27	33	15	75
Acute mania ..	7	4	1	—	12
Chronic mania ..	—	9	4	1	14
Post-leucotomy ..	—	1	—	—	1
Mental deficiency ..	—	2	2	—	4
Senile psychosis ..	—	7	2	—	9
Organic toxic confusional states (uraemia) ..	2	—	—	—	2
Post-epileptic confusional state ..	—	—	1	—	1
Totals ..	9	50	43	16	118

The group " much improved " comprises those patients no longer exhibiting excited or impulsive behaviour who have become more cooperative and generally exhibit a greater degree of social integration. It is in this group that improvement in insight frequently occurs. Delusions, if present, apparently cause little or no distress.

The " improved " group contains patients whose tendency to antisocial or excited behaviour is much diminished, who are quieter and better behaved than before treatment, and who are manageable without recourse to other therapeutic measures such as sedation or E.C.T.

Serpasil proved valuable in averting the onset of catatonic excitement in three chronic patients exhibiting typical prodromal symptoms, which in the past inevitably heralded the onset of episodes of excited, disturbed behaviour.

Therapeutic results are summarized in the accompanying Table.

Discussion

Serpasil has many advantages as a psychiatric therapeutic agent not possessed by the standard methods of treatment in current use. Its valuable sedative action, achieved in a setting of clear consciousness and free from the inhibiting effects commonly associated with the barbiturates, or the disorganizing effect on the higher brain functions of E.C.T., is of the utmost value in establishing rapport with patients. By means of its relaxing and calming action, anxiety and tension are diminished. Patients under its influence exhibit greater spontaneity, tend to be more sociable and optimistic and as a result are more accessible to psychotherapy and in a better condition to respond effectively.

Following treatment with " serpasil ", hyperactive, aggressive, and resistive patients tend to become quiet and cooperative. Nursing care and necessary tasks, such as feeding, dressing, and bathing, are no longer so arduous and depressing. Arising from improvement in behaviour, the need for measures such as barbiturate sedation or repeated courses of E.C.T. is lessened.

The administration of " serpasil " is relatively simple and side-effects are of minor significance. The use of the drug may be continued for long periods with little or no risk and only minimum supervision is required.

The drug proved a useful addition to therapeutic resources in cases reported here. Further research, however, is needed to establish more precisely the psychiatric conditions in which it is likely to be most beneficial and to investigate the possible modes of action.

Summary

Rauwolfia serpentina (" serpasil ") is an effective sedative for use in mental hospitals, although it is not equally effective in all cases. It reduces anxiety and drive and exerts a calming effect on psychomotor excitement. Patients under its influence are more accessible to psychotherapy.

Acknowledgment is due to Ciba Laboratories Ltd. for furnishing " serpasil "; Dr. A. R. Grant, Medical Superintendent, for permission to publish; and the nursing staff, Whittingham Hospital, for their co-operation.

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BOOK REVIEWS

The Role of Humoral Agents in Nervous Activity. By Bruno Minz. (Pp. viii + 230 ; 50 figures. 55*s*. 6*d*.) Oxford : Blackwell Scientific Publications. 1955.

The author of this short book has himself contributed original work in the field of " neurohumoral transmission ", and is still engaged on such research. The problems involved are therefore lively ones to him, and he succeeds in infusing the book with his own interest. After an historical review of the concept of humoral transmission from Langley and Loewi's work at the turn of the century, via Dale and Cannon to the researches of Feldberg and his contemporaries, he assesses the evidence for acetylcholine as a transmitter of impulses first in the autonomic system and then at the myoneural junction and in the central nervous system in general. In chapters dealing with cholinergic and adrenergic mechanisms he reviews the evidence for the site and method of action of acetylcholine and epinephrine. Inevitably acetylcholine, which seems to be widespread in many other tissues than the nervous system and which seems able to play some part both in conduction in fibres as well as at synapses, gets the lion's share of consideration : indeed, the book might almost be called " the role of acetylcholine in nervous activity". However, Professor Minz presents a fair summary of the sometimes conflicting evidence on such problems as the methods and agents responsible for humoral transmission and the role of electrical as opposed to chemical mechanisms in this field. It is clear, concise, and readable, and will be of value both to students of neurophysiology and to clinical neurologists who wish to refresh their knowledge in this sphere.

Prefrontal Leucotomy and Related Operations. By Alfred Meyer and Elisabeth Beck. (Pp. 60 ; 20 illustrations and 18 tables. 10*s*. 6*d*.) Edinburgh : Oliver and Boyd. 1954.

This represents a further contribution from the Department of Neuropathology at the Maudsley Hospital to the problem of correlating clinical and other changes with the anatomical lesion produced by operations on the frontal lobes. One hundred and two cases are reviewed of which no fewer than 62 had a full neurohistological investigation. The purely anatomical findings are of great interest and value.

Such facts as the presence of hypothalamic connexions of those parts of the thalamic nuclei which project to the medial orbital and cingular region, and the confirmation of a small direct efferent pathway from the granular prefrontal cortex to the hypothalamus must have implications for normal and abnormal cerebral function. So far as clinico-anatomical correlation is concerned, the evidence, as in their earlier studies, still seems to favour some relation between the quantity of frontal lobe isolated and clinical improvement, though a localizing factor plays some part, since section of dorso-lateral white matter seems to be much less important for recovery than mid-central, orbital, or cingulate. In an appendix of tables, summaries of clinical details and site of lesion are given for each case. This allows the reader to check the authors' conclusions and to draw others for himself if he wishes.

An Introduction to Physical Methods of Treatment in Psychiatry. Third edition. By William Sargant and Eliot Slater. (Pp. xix + 351 ; 2 plates. 20*s*.) Edinburgh and London : E. & S. Livingstone. 1954.

This edition is approximately half as big again as its immediate predecessor (1948). The chapter on prefrontal leucotomy and its applications has more than doubled in size, and there is a substantial new chapter on the treatment of alcoholic addiction. The bibliography has increased from 134 references to 344—an indication not of omissions in the previous edition but of the large volume of current work on relevant topics which the authors have neatly woven into the pattern of their text.

Happily, the book retains its original form and character, which gave it its appeal and won for it an established position as a practical guide for those who themselves perform the various techniques of physical treatment. The text is thoroughly up to date and includes, for example, brief discussions of treatment by chlorpromazine, acetylcholine, myanesin, and non-convulsive electrical stimulation of the brain. Dr. Denis Hill contributes, as previously, a chapter on the epilepsies, which embodies clear and concise advice on the selection of patients suffering from temporal lobe seizures who are suitable for surgery, as well as an enlarged summary table of the newer anticonvulsants.

It would have been helpful to have had fuller details of the dosage and spacing of penicillin in the treatment of general paralysis.

Some may be surprised to find an apparent leaning towards unmodified E.C.T. as a standard practice, and restricting the use of a general anaesthetic and muscle relaxant in this treatment to special cases. Not everyone will regard the argument in favour of this as being quite as convincing as the statistics quoted may seem alone to suggest, but it may be intended to apply only if the services of a skilled anaesthetist are not available,

in which case few would dissent from it. The point is of sufficient importance, in a treatment so widespread, to merit some clarification in future editions. The authors might consider it worth while to include some observations on hypotension as well as hypertension among the conditions that may indicate special hazards in E.C.T. However, it is hardly the function of a review to weigh the pros and cons of authors' recommendations, but rather to indicate the status, reliability, and value of the work in question for the purpose which it sets out to achieve. On this score, there can be no doubt that " Sargant and Slater ", as it has come to be known colloquially—one had almost said affectionately, for it is a most likeable book—continues to be of the first rank.

Intracranial Gliomata. Some Clinical, Radiological, and Therapeutic Aspects of 298 Cases. By John Penman and Marion C. Smith. (Pp. 69. 5*s*.) M.R.C. Special Report Series No. 284. London : H.M. Stationery Office. 1954.

The cases analysed in this monograph were seen in a single neurosurgical clinic and radiological treatment was given either at this or at one other hospital. Thus all received equally competent diagnosis and surgical and radiological treatment, and from this aspect form a very suitable group for study. They have been carefully analysed from many points of view, including the sex and age of the patients, the symptomatology, the site and nature of the tumour, and the treatment received. From this analysis the authors draw certain conclusions which, although rendered tentative by the comparatively small number of patients, appear to be quite unbiased and fully justified by the analysis. That they are not always in accord with modern teaching makes them all the more important since re-assessment of the results of treatment of intracranial gliomas is overdue.

The sex incidence of intracranial gliomas was found to be less strongly biased towards males than in some earlier series. In childhood males and females were equally affected, but in the earlier years of adult life the incidence rose to nine males for every five females. Epilepsy was a symptom in 43·4% of all cases and in 32·3% was the first symptom ; eight out of 11 patients with oligodendrogliomas had epileptic attacks but in only half of these were they the first symptom. Headache was predominantly unilateral in 25% of cases in which a glioma was confined to one hemisphere, and in 84% of these cases was on the side of the tumour. Duration of symptoms before admission to hospital was found to have no relationship to length of survival after treatment, but, as might be expected, there was here a close correlation with epilepsy. Of 40 patients with a history on admission of more than 24 months, 35 had had epileptic fits.

Operative treatment was, of course, important, and resulted in apparent cure in nearly 75% of all cases of cerebellar astrocytoma. In tumours of the hemispheres the results were less good, and surgery appeared to be valueless in tumours of the brain-stem and corpus callosum. An unexpected result of the analysis of results in tumours of the hemispheres was that length of survival was more closely correlated to the age of the patient than to the malignancy of the tumour. Thus 40% of cases with astrocytomas and 20% of those with glioblastomas survived for more than three years from the onset of symptoms, but in both types of tumour 59·3% of patients under the age of 40 survived for this length of time as against only 12% of those over this age.

In assessing the results of radiological treatment the authors exclude all cases dying within three months of admission to hospital. The remaining numbers are too small to permit of definite conclusions. There were however 21 patients treated by brain puncture (diagnostic surgery) alone followed by radiotherapy and, of these, six survived for more than 12 months. Excluding cerebellar astrocytomas, which did well whether or not they were treated radiologically, 16 cases were treated by major surgery alone, with seven survivals for more than 12 months ; 86 were treated both by major surgery and irradiation with 29 survivals.

Clearly no indication can be gleaned from such small numbers as to the best line of treatment ; this must still be decided by the nature of the case. The analysis shows, however, that our knowledge as to the type of case which is likely to benefit from radiotherapy is still rudimentary, and justifies the authors' demand for the use of more adequate controls in any further assessments of the value of *x*-ray treatment.

Diencephalon : Autonomic and Extrapyramidal Functions. By W. R. Hess. (Pp. 79 ; 33 figures. 25*s*., $4.00.) London : William Heinemann ; New York : Grune and Stratton. 1954.

It is possible that, among English-speaking neurologists, the work of Hess of Zurich is more often praised than read. This short introductory monograph deserves a very warm welcome. It summarizes findings already reported in 122 publications, and promises that the original material—protocols, films, and brain sections—will remain available to interested experts. Stimulation or destruction of accurately defined regions of the hypothalamus in the waking and unrestrained cat, by a refined method, reveals overlapping territories concerned in autonomic and postural reactions. Of these, the induction of natural curling up for sleep is still the most remarkable. From the tectum, movements of head and eyes, related to the representation of different parts of the visual field, are excited. " The frequently expressed hypothesis which coordinates individual signs or functions with individual nuclei cannot be verified ". For Hess, a nervous centre is " a device to establish connexions. . . . Nervous elements located at very different levels of the nervous system may constitute a centre. . . . A centre is represented by series of polysynaptic connexions from among which—under the controlling influence of the peripheral situation—those connexions are selected which give the appropriate pattern of a directed motion ". The theme of the research is the integration of the autonomic reactions, by which the internal environment is stabilized, with the somatic reactions of the animal to its surroundings.

Röntgendiagnostik des Schädels. By W. Loepp and R. Lorenz. (Pp. xvi + 579; 696 illustrations. DM. 97.–.) Stuttgart: Georg Thieme Verlag. 1954.

This book is an important addition to the study of the skull in relation to disease. Much of the material presented was collected with great perseverance by the late Professor Willy Loepp, who had a life-long ambition to write a textbook on craniology.

After Loepp's death in 1950 Professor Reinhold Lorenz undertook to complete this study.

In addition to the neurologically familiar aspects of skull radiography, there is a comprehensive account of skull development, defects and faults in growth, the various dysostoses, skull reaction to endocrine disease, to metabolic diseases, and to infection. Skull injuries and intracranial diseases occupy large sections, and special attention is given to intracranial calcification. Diseases of the jaws, nasal sinuses, and teeth all receive detailed consideration.

Modern methods of encephalography have tended to distract attention from the importance of the pure radiographic study of the skull, and this remarkable book will be welcomed as an invaluable work of reference on a very vital part of radiological diagnosis.

Verstehen und Einfühlen. By H. W. Gruhle. (Pp. vi + 458. DM. 29.60.) Berlin: Springer Verlag. 1953.

In this attractively produced volume we are presented with the collected papers of one of the greatest teachers and clinical investigators of the "phenomenological" school of psychiatry which developed in Germany at the end of the Kraepelinian epoch. The achievements of this school were of great importance, leading to the clarification of concepts, the distinction of pathological processes from modes of psychological reaction, and the provision of refined and reliable methods of diagnosis depending entirely on bedside observation. In this field Gruhle was a leader, and his work was marked by fertility of ideas, an intuitive understanding of the minds of his patients, and a gift for lucid and graphic description. The principal tool of investigation was "Verstehen und Einfühlen", understanding and empathy, which gives the title for the book; used in a self-conscious and self-critical way, it provided the main standard by which pathological mental processes could be distinguished from those which, however abnormal, yet did not indicate disease. The fruits which fell to this work are exemplified by the succession of papers: "The Significance of Symptoms in Psychiatry" (1913), "The Psychology of Schizophrenia" (1922), "Psychopathy and Psychosis" (1932).

This collection of his papers, made at the end of his professional life, shows also, what might well have been forgotten, the very wide range of Gruhle's interests and the extent of his contributions outside the range of the psychoses, to the psychology of the normal and the psychopathic, to criminology and forensic psychiatry. The author's very attractive style makes his papers as fresh and lively now as at the time they were written.

Clinical Psychiatry. By William Mayer-Gross, Eliot Slater, and Martin Roth. (Pp. xiii + 652; 16 plates. 50*s*.) London: Cassell & Co. Ltd. 1954.

British reaction to the resurgence of psychodynamic concepts, especially in U.S.A., has been growing for some time; it will receive impetus from this book. The authors consider that psychiatry suffers from sectarianism, unwarranted attempts to expand its scope, and the danger of being divorced from the parent science of medicine. They plead that "the natural corrective to these unhealthy tendencies is supplied by a return to the bedside and to the discipline of clinical observation".

After reviewing contemporary schools of psychiatry, a multi-dimensional approach is suggested. One of the main differences between this and the Meyerian psychobiological approach is the emphasis that is laid on the similarities among individuals composing a clinical group rather than on the differences in their personal biographies and the minutiae of the reactions of their personalities. This leads naturally to the search for specificity in causation, symptomatology, and treatment, but does not deny the cumulative influence of non-specific factors and the colouring of specific syndromes by individual personality reactions. Thus are the authors led to speak of scales of reference and dimensions by which causal factors and clinical data can be compared. The reader might be more ready to accept this as the path of psychiatric virtue (or at least one worth trying) if the authors showed more moderation in their criticism of other schools of thought. In this, as in their criticism of British psychiatrists before the First World War, many will think their assertions much too sweeping and not always as well informed as they might have been.

However, when the real core of the book—the description of the various clinical syndromes and guidance about how to manage and treat them—is reached, the authors come into their own, and the reader cannot fail to discern the sure touch and sound judgment of the experienced and knowledgeable clinician.

A sharp distinction is made between personality reactions on the one hand and formal process illness on the other. Thus, various neurotic and psychopathic reactions of most diverse kinds are grouped together in one chapter, whereas affective disorders, schizophrenia (with the paranoid disorders), and many particular organic syndromes are given chapters, or substantial sections of chapters, to themselves, as are the mental diseases of the aged and of children. This tendency to present the subject in part on a basis of clinical description, in part on a basis of age groupings, leads to a certain amount of repetition. The chapters dealing with the marginal territory between neurology and psychiatry are excellent, and there is a compendious account of chemical intoxications and addictions quaintly sub-titled "Pharmacological Psychiatry".

Administrative and legal psychiatry is discussed conceptually rather than in terms of detailed practical instruction, and comparison is made in procedural differences in various countries. There are one or two slips concerning British procedure, for example (p. 548); recommendations, not certificates, are required for tempo-

rary treatment, one of the main points of this procedure being the avoidance of certification ; and the approved practitioner who is required to sign one of the recommendations need not in fact be a specialist.

The number of plates is unusually large for a psychiatric textbook. They illustrate physique in Kretschmerian and Sheldonian terms ; the neurological concomitants, pathological and symptomatological, of some mental diseases ; and the grimaces and postures of a schizophrenic. Bibliography is abundant for the text, though not itself inherently compendious.

Psychosomatic disorders do not bulk largely in this book. The authors appear to be more concerned with what medicine can do for psychiatry than with what psychiatry can do for medicine—many will think rightly so in the context in which their ideas are expounded. The finer points of deciding the general strategy in treatment of the individual syndromes are remarkably well expounded, though for the details of the carrying out of treatments the reader is clearly expected to refer to other works.

The authors have succeeded in producing a work that has been needed for a considerable time in Britain —namely, a textbook of psychiatry for psychiatrists. Although they aim at providing for the needs of the student, the general practitioner, and the non-psychiatric medical specialist too, it is undoubtedly to the advancing student of psychiatry that this book will make its greatest appeal. Although it is not free from flaws of the kind already indicated, it can only be regarded as a major work of the first class.

Peripheral Nerve Injuries. Medical Research Council Special Report Series No. 282. (Pp. 451. 55*s*.) London : H.M.S.O. 1954.

During the Second World War five nerve injuries centres were established in Britain as part of the Emergency Medical Service, and in connexion with these centres the Nerve Injury Committee of the Medical Research Council supported a variety of research projects the results of which are described at length in this volume.

The main basis of these reports depends on an elaborate and uniform plan of case recording. This provides a large mass of material for analysis of clinical features such as variations in innervation, trophic disorders, rate of axonal re-growth, degree of functional recovery, and the results of various surgical procedures. In this connexion, the successful results of nerve grafting reported by Mr. Seddon are of special interest. From the Unit in Edinburgh, R. L. Richards reports some important clinical studies on the vasomotor and nutritional disturbances after nerve injury, and a specially authoritative section on neurovascular lesions and on various forms of ischaemic paralysis.

The section on causalgia from Glasgow by Barnes will be read with interest, for it analyses the therapeutic value of sympathectomy, and it is suggested that in causalgia an artificial synapse is established between the sympathetic and somatic afferent nerves. This study is, however, disappointing in that it does not include sufficient studies of somatic nerve block, vasomotor responses, which are now used so much to study abnormal pain thresholds.

From the clinical research point of view some of these reports are disappointing. Perhaps the heavy burden of detailed case recording may have stifled ideas for breaking new ground that must have occurred to the specialists working on the subject. The failure to use an accurate method of muscle strength measurement prevents the adequate study of muscle recovery. The experimental work on the behaviour of denervated muscle is inadequate as regards the study of fibrosis, shortening and response to electrical therapy. The possibility of drugs such as prostigmine influencing the recovering neurone has not been investigated.

In regard to rehabilitation, there must be a mass of information regarding the use to which a partially denervated limb can be put which would be of considerable practical value, but in this regard the degree of functional recovery is little considered. The problem of nerve injuries as they appeared to the Armed Forces is not discussed. The common neurotic complications of nerve injury and the psychological aspects of the rehabilitation of these cases receive little consideration.

However, though there are very obvious gaps in these reports, all who are interested in nerve injuries will welcome this volume as a book of reference to the subject and as a record of a very painstaking and useful wartime organization.

Introduction Historique à l'Étude des Néologismes et des Glossolalies en Psychopathologie. By Jean Bobon. (Pp. 344. Fr. frs. 2,015.–) Paris : Masson & Cie ; Liège : Vaillant-Carmanne. 1952.

In its limited field, this book is likely to prove a classic. In strict historical sequence the author gives a detailed résumé of all the contributions to the study of neologisms from 1852 to 1936. These works are almost exclusively of the clinical descriptive kind, often with emphasis on the linguistic derivation of the neologisms or neologistic systems employed by the patients, and with interpretation along psychological, psychopathological, or psychoanalytic lines. The efforts which have been made at systematic classification of modes of disturbance have not gone very far, and in only the rarest cases was it possible to relate clinical symptoms with brain pathology. The great majority of patients in whose speech neologisms abound, or neologistic systems so constant and elaborate as to amount to a new language (glossolalia), have been schizophrenics. The resemblances and differences between schizophrenic speech disorder (schizophasia) and phenomena shown by the normal, in states of distraction or fatigue, hypnagogic and dream states, by children, primitive races, by hysterics, epileptics, manics, the confused and delirious, and organic paraphasics, have been repeatedly analysed in attempts to define psychological mechanisms. At the end of the résumé of each successive work the author confines his critical comments to a single paragraph, but at the end of the main part of the work he has a final chapter of conclusions of 13 pages.

In this he classifies schizophrenic speech disturbances into neologisms, paralogisms, agrammatisms, paragrammatisms, glossolalia and glossomania ; somewhat similar terms may be used to classify disturbances of the written language, and disturbances of mimetic language have so far hardly been studied at all. All these forms of disturbance, it is claimed, may be grouped into those which derive from deficits, and those which are positive and reactive. In the examination of the first, Jacksonian concepts may be employed, it being held that with interference with higher regulatory and inhibitory controls simpler functional forms are released, with such mechanisms as perseveration, contamination, substitution, and mutilation. On the adaptive and compensatory side there is evidence that neologisms are at times manifestations of psychologically much more complex phenomena. Thus they may be used by the patient to refer to experiences, concepts or ideas, occasioned through the psychosis, for which there are no words in normal parlance, or used as a code word to conceal what is being said from imagined persecutors, or used because of an imagined magical power. The playful use of neologisms has also been repeatedly observed. The author proposes, in addition to this duality, a duality of modes of research; the mechanistic, relating speech disturbances with neurology, and the anthropological, relating them with the psychologically primitive, with the speech of children or primitive languages.

The History and Development of Neurological Surgery. By Ernest Sachs. (Pp. 158 ; 50 figures. 30*s*.) London : Cassell & Co. 1953.

Dr. Sachs is particularly well qualified to write a history of neurological surgery ; as Dr. Fulton states, he " has lived through and contributed to the heroic age " of this branch of surgery. He provides a living link with the founder of neurological surgery, for in 1909 Dr. Sachs spent two years working with Sir Victor Horsley, and only retired from the Chair of Surgery at St. Louis in 1949.

This book will interest many besides neurosurgeons, for Dr. Sachs has interpreted his subject broadly. There are continual references to the state of knowledge at different periods of time in the basic sciences, and in other branches of medicine and surgery, which enable the reader to keep the particular aspects of neurological surgery in proper perspective. Some of the observations are quite fascinating. Rude craniotomies were carried out in neolithic times, and it seems clear that patients survived although nothing is known of the empirical methods—if any—for avoiding or controlling infection. It may be that bacterial population and virulence have progressed hand-in-hand with human population. The first observations that damage to one side of the head affects the opposite limbs were found in Egyptian records of about 3000 B.C. Dr. Sachs quotes a graphic account of an attack of temporal epilepsy, with descriptions of visual and olfactory hallucinations, and behaviour disorder—" they are passionate and unreasonably peevish "—given by Aretaeus, a Greek physician who lived at Rome during the second century A.D. We learn also that he described the group of symptoms which are now ascribed to lumbar disc protrusion, and subdural haematoma. In the section on modern neurological surgery inevitably the subject matter becomes more restricted to surgery and pathology and deals with the manner in which various problems have been overcome. In his preface Dr. Sachs disarms criticism because he admits to some undue emphasis on the American literature. Nevertheless one would have liked to see a little more credit given to some of the leading British neurosurgeons. The book is liberally illustrated, and a particularly interesting photograph is that of a group of members of the Second International Neurological Congress (1935). It is a pity that the key to this does not include all the names, and that of Lima is applied to the wrong person.

This is a book that can be read with pleasure by all interested in medicine, surgery, and the basic sciences, and its value is enhanced by a large bibliography.

The Origins of Psycho-Analysis. Sigmund Freud's letters to Fliess. (Pp. 445. 30*s*.) London : Imago Publishing Co. 1954.

Whether we like it or not, Freud and Marx condition the intellectual climate in which we live probably more than any other two figures of the past century. Of the two, Freud's influence is likely to be the more far-reaching ultimately, and it is therefore a welcome decision of his family, despite his own decided views to the contrary, that material such as family records and letters should be made available for biographical purposes. The present volume contains the lengthy correspondence, extending over some 15 years, of Freud to his friend Wilhelm Fliess, who had a large consulting practice in Berlin but whose medical and scientific interests extended far beyond his specialty as a nose and throat surgeon. The letters are all from Freud to Fliess as Freud himself destroyed all Fliess's letters to him. They form a fascinating and revealing commentary on Freud's intellectual and emotional development, and to a lesser extent on the life of the professional classes in the capital of the Austro-Hungarian Empire in its sunset period. In addition to the letters, there are drafts of Freud's early views on the aetiology of various psychiatric symptoms such as anxiety, melancholia, and paranoia, and a lengthy " Project for a Scientific Psychology ". The book therefore certainly fulfils the promise of its title in showing us Freud's mind at work at a time when he was feeling his way towards the comprehensive theory and practice of psychoanalysis. To many, however, its interest will lie in the picture it gives of a man of genius overcoming the difficulties of his own personality and of his environment—the highly organized system of influence and patronage that lay behind the " gemutlichkeit " of Franz Josef's Vienna.

The Cerebrospinal Fluid. By S. Lups and A. M. F. H. Haan. (Pp. xv + 350 ; 93 figures. 52*s*. 6*d*.) New York : Elsevier Publishing Co. 1954.

As Professor Bailey says in his introduction, a new monograph on the cerebrospinal fluid is badly needed.

It is therefore the more disappointing that this book, which looks so promising in its scope and general arrangement, should have so many faults. It contains a large amount of essential information, together with a remarkable collection of curves from colloidal reactions in different neurological conditions. The bibliography also is adequate, if not quite so up to date as might have been hoped. But as a whole the book is marred by a certain confusion in both terminology and thought. Further, dogmatic statements are often made on controversial matters, and frequently without reference to the relevant authority. For example, it is clear from the body of the text that by the " lumbar pocket " (or, as it is printed in one place, the " lumbar socket ") is meant the spinal subarachnoid space. Yet in the anatomical section this " pocket " is described as extra-arachnoid. Again, the term " communicating hydrocephalus " is not commonly used in the sense of over-production of cerebrospinal fluid by the choroid plexus. A similar confusion is only too apparent throughout the long and important section on the meningitides. Finally, in the section on methodology no indication is given of the error of the methods described ; and in at least one instance—that of the bromide estimations required for Walter's test—the method described is obsolete. In brief, then, this book is useful to those specially concerned with the problems of the cerebrospinal fluid ; but for the clinical neurologist it will not supplant the other monographs.

Aspects of Cerebellar Anatomy. Edited by Jan Jansen and Alf Brodal. (Pp. 423 ; 92 figures. Price not stated.) Oslo : Johan Grundt Tanum.

This volume is a collection of essays written by the members of the Anatomical Institute at Oslo in honour of their former teacher, Professor K. E. Schreiner. An important feature of the book is that it is based to a very large extent on the results of the authors' own researches over the last two decades. The afferent and efferent connexions of the cerebellum in particular are treated very thoroughly, and problems of localization within these projections, as well as the relation of cerebellar structure to function, are discussed in the light of recent work based on more specialized techniques. Other subjects dealt with include the morphology of the mammalian cerebellum, the descending connexions of the inferior olive, and the development of the rhombic lip and its derivatives. The extensive and up-to-date review of the literature should further enhance the value of this work as a reference book for all neurologists.

The Study of the Brain. By H. S. Rubinstein. (Pp. xiii + 209 ; 43 plates. $9.50.) New York : Grune and Stratton. 1953.

In this small textbook the author first gives the student detailed instructions for dissecting the brain, and at suitable stages discusses the structure and function of the part under consideration. In this way an interesting presentation of functional anatomy is built around the exercise of dissection.

Cerebrovascular Disease. By Peter Murphy. (Pp. 408 ; 128 figures. 90*s*., $12.00.) Chicago : The Year Book Publishers ; distributed in the U.K. by Interscience Publishers, London. 1954.

This book of some 400 pages clearly aims at a comprehensive treatment of the subject. It ranges from the embryology of the cerebral blood vessels to the rehabilitation of the patient who has had a stroke. Discussion of such a widespread field inevitably means that some subjects have to be treated with the brevity that suggests dogmatism, and where clinical information is given in tabular form an unreal simplicity is often introduced. Nevertheless, the book contains a great deal of well authenticated information.

The introduction, by way of embryology, anatomy, and physiology before the clinical side is mentioned, is a welcome encouragement to interpret signs and symptoms in terms of the basic sciences. The author clearly believes in vasospasm, and marshals the clinical and experimental evidence in its favour, though he does not really meet the objection that spontaneous vasospasm in apparently healthy cerebral arteries is a less likely explanation than others for some of the " vasospastic " syndromes.

In general this book will be valuable as a reference work (its treatment of the literature is adequate and up-to-date), especially to neurologists who may be unfamiliar with recent work in the cardiovascular field.

Frontal Lobes and Schizophrenia. By Milton Greenblatt and Harry C. Solomon. (Pp. xi + 425 ; 35 figures. £4 10*s*.) New York : Springer Publishing Company ; London : Lange, Maxwell & Springer. 1954.

This book is the second report of the findings of the Boston Psychopathic Hospital in operations on the frontal lobes for the relief of mental illness. One hundred and sixteen cases are reviewed and the results of three procedures are considered : full bilateral leucotomy, bimedial leucotomy in which only the medial aspects of the frontal white matter are cut, and full unilateral leucotomy. The authors conclude that bimedial operations give the best results in the average chronic psychotic. This is of some interest since the cut must involve the connexions of the cingulate gyrus and some parts of what Papez has called the neurological substrate of emotion. The full bilateral operation seems to be unnecessarily extensive and tends to produce unwanted reduction in drive and initiative, while the unilateral operation gives insufficient relief of such symptoms as tension. However, it is interesting that results suggest there is always some change, e.g., measurable reduction in anxiety, following the unilateral cut, and, so far as the figures indicate, changes are more marked with operations in the right (non-dominant) hemisphere. Evidence also emerges that autonomic changes, especially in blood pressure and pulse rate, usually follow these procedures which tends to confirm the view that the frontal lobes are concerned with autonomic function. Clinical, physiological, psychomatic, and sociological studies were all used in assessing results and the book contains many useful facts, but the style is turgid and it is difficult to read.

Connections of the Frontal Cortex of the Monkey. By Wendell J. S. Krieg. (Pp. xi + 299; 186 figures. 75*s*. 6*d*.) Springfield, Ill.: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 1954.

This book comes from the late Professor Ranson's Anatomical Institute at the North-Western University and therefore carries a certain neuro-anatomical imprimatur. It contains the anatomical findings following 70 discrete localized lesions at varying points of the frontal cortex of *Macaca mulatta*, and the author's claim to have "presented the most detailed set of observations that have ever been accumulated on the connexions of the frontal cortex" is probably justified. The topographical nomenclature used is that of Brodmann and the Vogts, with further sub-areas defined by the author.

The book contains a large mass of anatomical facts which are likely to be of direct value to the specialist, and also to suggest possible correlates with the human brain for the clinician. In this connexion the preponderance of backward (parietal) over forward association fibres from frontal areas is interesting, while the absence of any cortical connexion with the caudate nucleus, putamen, or pallidus is worth noting. All the evidence is derived from Marchi studies, and no use was made of other stains, particularly the various modifications of the silver techniques now generally employed. The illustrations are a special feature of the book, particularly the author's method of portraying his findings from serial sections as a transparent three-dimensional reconstruction of the part examined.

Die Wirbelsäulen-Verletzungen und ihre Ausheilung (Vertebral Injuries and their Repair). By Alfons Lob. (Pp. xii + 272; 149 figures, 16 tables. DM. 78.–.) Stuttgart: Georg Thieme Verlag. 1954.

This monograph is based on the author's experience of fractures and fracture-dislocations of the spine, on a total material of over 400 cases, 51 of which resulted in paraplegia.

In the first chapter of the monograph, the author deals with the anatomy and physiology of the spine, the mechanics and classification of vertebral injuries and their pathology affecting the various levels of the spine.

In the second chapter, which represents the most important part of the book, the author gives details of the pathological changes of both the osseous and cartilaginous structures of the vertebra, occurring during the various stages of repair, following spinal injuries. Particular attention is paid to the traumatic changes of the intervertebral disc, in relation to callus formation of the vertebral body. This chapter is particularly well illustrated with photographs of anatomical preparations and radiographs.

In the following chapter, which deals with the treatment of spinal injuries, the author's approach to spinal injuries, both with and without cord involvement, is conservative. He obviously does not agree with the method of closed reduction, as advocated by Boehler as the method of choice in the treatment of these injuries, and he emphasizes the dangers of this method in causing paraplegia or increasing neurological symptoms, which, at the time of injury, were only slight. As far as surgical procedures are concerned, he is not in favour of internal reduction and stabilization of the broken spine by graft (Albee), and no mention is made of the method of internal fixation by metal plating. Laminectomies are considered unnecessary in most spinal injuries with cord involvement. With regard to treatment of traumatic paraplegics, he refers to the progress made in this respect in England and advocates the establishment of spinal centres in Germany.

The last chapter deals with the legal aspects of spinal injuries involving the normal spine, as well as those of the abnormal spine caused by congenital, infectious, degenerative, or vascular processes.

This book can be recommended to everyone who is interested in traumatic disorders of the spine.

The Diagnosis and Treatment of Convulsive Disorders in Children. By Samuel Livingston. (Pp. xx + 314; 71 figures. 69*s*.) Springfield, Ill.: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 1954.

This book is based on the clinical material of the Johns Hopkins Epilepsy Clinic and is therefore to some extent a companion volume to E. M. Bridge's "Epilepsy and Convulsive Disorders in Children". The present work is, however, directed especially to a general practitioner audience and does not therefore carry much of the authoritative information that makes Bridge's book invaluable for reference to neurologists and paediatricians. Even allowing for its intended audience, the book seems unsatisfactory in mentioning too many subjects too briefly. This is especially marked in the section on "Social Management". Again a wide variety of drugs is mentioned but sometimes so shortly that no idea is gained of their possible place in the treatment of a given case. The dangers and difficulties occasionally met with in the established case of status epilepticus seem unknown to the author. The results claimed for the ketogenic diet are rarely achieved in this country, probably because it is not pursued so consistently and thoroughly as in the cases reviewed.

A more fundamental criticism is of the author's use of terms. He considers cryptogenic or idiopathic epilepsy separately from secondary epilepsy due to proven brain damage or disease but then discusses a third group of "disorders simulating epilepsy", such as breath-holding attacks, febrile convulsions, hypoglycaemia, etc., all of which may lead to a symptomatic convulsion through similar physiological mechanisms to those involved in his secondary epilepsy. In a further chapter on "Precipitating Factors" the influence of sleep, emotional upset, fatigue, fever, water balance, are mentioned in relation to cryptogenic epilepsy. However, these features may also trigger "secondary epilepsy", while some of them could just as well be considered as "disorders simulating epilepsy".

These strictures do not apply to the chapter on electroencephalography, which forms an excellent and well-balanced introduction to this subject, useful for general practitioners, students, or medical specialists unacquainted with the technique.

Développement Psycho-Moteur du Premier Age. By Cyrille Koupernik ; illustrations by D. Harlé. (Pp. 197 ; 58 figures, 7 tables. Fr.fr. 500.–.) Paris : Presses Universitaires de France. 1954.

" Mental hygiene begins in the cot ", concludes the author, but this book in support of his conclusion seems to fall between two stools. On the one hand he sets out to provide a lengthy description of the developmental stages which are seen in the baby from birth up to the beginning of the third year, together with the tests by which these may be recognized ; on the other, to argue that some aspects of mental illness, notably schizophrenia and depression, have their origins in infantile problems of maturation. These two themes get rather involved and the argument is difficult to follow in places.

Essentials of Abnormal Child Psychology. By Ernest Harms. (Pp. xiv + 265 ; 43 illustrations. $5.00.) New York : Julian Press Inc. 1954.

The author is the editor and publisher of the well-known periodical *The Nervous Child* and is a practising child psychotherapist. He was trained in Europe under Kraepelin before he came under the influence of Freud, Adler, and Jung, and it is principally from Kraepelin and from Jung that his basic ideas are derived. The result is a book which is highly interesting, original, simply written, temperate, and free from fanaticism. The first half is concerned with an outline of his approach, with essays on special clinical problems, such as schizophrenia and hysteria in childhood ; the second half describes techniques both of diagnosis and treatment which, apart from the author's personal contribution, are broadly based and eclectic. There is an abundance of case reports, which illustrate the author's common-sense methods of handling his patients.

The title of the book has, perhaps, been badly chosen, as it suggests to the reader that there is here a systematic even if abbreviated survey. This is not the case. The greater part of the work consists of chapters on isolated problems, without any organic connexion with one another, and it is only in the part devoted to treatment that the material is handled in a more systematic way. Nevertheless the student of child psychiatry can learn much.

Recent Developments in Psychosomatic Medicine. Edited by Eric D. Wittkower and R. A. Cleghorn. (Pp. 495. 50*s*.) London : Sir Isaac Pitman.

The term psychosomatic medicine suggests an attempt to integrate psychic and somatic factors in disease : but the attempt runs into difficulties similar to those that have always beset the relationship of mind and brain. Psychosomatic medicine has avoided the difficulty by developing simply as an extension of psycho-analysis in which somatic symptoms are considered as manifestations of a psychopathology. This has certainly not achieved much integration, and has made the subject rather lop-sided. In this book a welcome tendency to correct this concept can be seen. It consists of 25 articles by 28 authors. Their quality is uneven. Those which deal with research and experimental approaches and with the possible cerebral mechanisms involved in psychosomatic reaction have a freshness and interest which are lacking in the more purely clinical discussion.

The concept of psycho-social disease is briefly discussed. The problem of specificity of psychosomatic disease is considered, but only to be dismissed since " deep analysis leads . . . to the common origin of the neurotic process " and " seemingly sharp differences in symptoms are relatively superficial vagaries ". However, the problem has some practical importance—the difference, for instance, between migraine and ulcerative colitis as psychosomatic reaction patterns involves a considerable difference in morbidity and even mortality. Unfortunately, the style of writing, quite apart from the use of technical jargon, is at times verbose, prolix, and wearisome.

Heredity in Health and Mental Disorder. By Franz Josef Kallmann. (Pp. 315; 89 figures. 42*s*.) London : Chapman and Hall. 1953.

The subtitle of this work, " Principles of Psychiatric Genetics in the Light of Comparative Twin Studies ", gives a better idea of its contents than the main title. The author is a clinical psychiatrist who has devoted his life to the investigation of problems of psychiatric genetics, using the method of studying twins and their families as his main tool. His work was honoured by the invitation to give the 1952 series of Salmon Memorial Lectures, which have now appeared in the present book form.

In effect, the book is designed as an introduction to psychiatric genetics suitable for study by the medical student and the medical and psychiatric clinician. It is divided into three parts, the first giving an elementary exposition of genetics and the methods of genetical study suitable to man, the second part an account of the results attained, and the third a discussion of the significance of genetics for mental health planning. It is in the second part that the author is particularly at home, and the part which will be most valuable for the majority of readers.

The importance of genetical aetiological factors in practically all psychiatric disorders can hardly be overstated. The author is in a position to provide detailed discussions from this point of view of the psychopathies and neuroses, manic-depressive, schizophrenic, involutional, and senile psychoses, convulsive disorders, and mental deficiency. In some of these conditions his own work provides the most important contributions we have. To list only some of the most significant figures, Kallmann has found that the concordance rate in uniovular twins, i.e., the proportion of cases in which both members of a twin pair were found to suffer from the same illness, was in male homosexuals 100%, in manic-depressives 100%, in schizophrenics 86%, in involutionals 61%.

The book is profusely illustrated with tables and figures and photographs of twins, the last being particularly interesting when the author is discussing the significance of bodily constitution.

A Methodological, Psychiatric and Statistical Study of a Large Swedish Rural Population. (English translation.) By Tage Larsson and Torsten Sjogren. (Pp. 250. Sw. Cr. 25.–) Copenhagen : Ejnar Munksgaard. 1954.

This psychiatric and statistical study of a large Swedish rural population is a valuable book of references for anyone undertaking surveys of the kind described. The list of the references together with the notes of methodology are valuable in themselves. Two criticisms may be made forthwith : first, in regard to the title, it is hardly possible to conduct a methodological study of a population ; here and there too the text bears the mark of translation, but these criticisms together with certain points in the arrangement (for example, separation of the summary and conclusion would have made for easier reference) should not be allowed to obscure the essential value of the data collected. It has been collected with great care, and covers 45 years of registration in a partially closed community with about 25,000 inhabitants, among whom 1,312 cases of psychosis, severe psychopathy, low-grade oligophrenia, and suicide were found by going through the 13 relevant parish registers for the years 1900 to 1944.

The results are to be published in two parts : the present part deals with methods, the representativeness of the sample, results concerning age of onset of disease, time in hospital, mortality, morbidity risks in the general population, and the frequency of consanguineous marriages. No significant increase in the frequency of first-cousin marriages was found between the parents of psychotics, but there such was an increase among the parents of oligophrenics.

The second part of the report will deal with the results of family studies, in particular the morbidity risks for parents and sibs, and will give the clinical and genetic analysis of the material.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books recently received.)

Grundfragen der Neurosenlehre. By J. H. Schultz. (Pp. xii + 215. DM. 24.–.) Stuttgart : Georg Thieme Verlag. 1955.

Management of Addictions. By Edward Podolsky. (Pp. xvii + 413. $7.50.) New York : Philosophical Library Inc. 1955.

Hématomes Intracraniens d'Origine Traumatique. By Pedro Larghero. (Pp. 254 ; 114 figures. Fr.frs. 1,500.–.) Paris : Masson et Cie. 1955.

Neuroglia Morphology and Function. By Paul Glees. (Pp. xii + 111 ; 44 figures. 25*s*.) Oxford : Blackwell Scientific Publications. 1955.

Lectures on the Scientific Basis of Medicine. : Volume III, 1953–54. British Postgraduate Medical Federation. (Pp. ix + 398 ; 9 plates. 35*s*.) London : The Athlone Press. 1955.

Angiographic Localization of Intracranial Masses. By Arthur Ecker and Paul A. Riemenschneider. (Pp. xviii + 433 ; 413 figures. 97*s*.) Oxford : Blackwell Scientific Publications ; Springfield (Illinois) : Charles C. Thomas. 1955.

Traumatismes du Crane : Médecine—Chirurgie—Expertise. By Daniel Ferey. (Pp. 170 ; 90 figures. Fr.frs. 1,100.–.) Paris : G. Doin et Cie. 1955.

Klinische Psychopathologie. By Kurt Schneider. (Pp. 188. DM. 12.80.) Stuttgart : Georg Thieme Verlag. 1955.

The Abnormal Pneumoencephalogram, 2nd ed. By Leo M. Davidoff and Bernard S. Epstein. (Pp. 518 ; 696 illustrations on 291 figures. 110*s*.) London : Henry Kimpton. 1955.

Atlas of Consecutive Stages in the Reconstruction of the Nervous System, 1st ed. By Louis Hausman. (Pp. 83 ; 71 figures. 20*s*.) Oxford : Blackwell Scientific Publications ; Springfield (Illinois) : Charles C. Thomas. 1953.

Atlases of the Spinal Cord and Brainstem and the Forebrain, 1st ed. 1951, 2nd printing 1954. By Louis Hausman. (Pp. 63 ; 54 figures. 15*s*.) Oxford : Blackwell Scientific Publications ; Springfield (Illinois) : Charles C. Thomas.

Genetics and the Inheritance of Integrated Neurological and Psychiatric Patterns. Proceedings of the Association for Research in Nervous and Mental Diseases, December 11 and 12, 1953, New York. (Pp. xiv + 426 ; 77 figures. 76*s*. 6*d*.) London : Baillière, Tindall and Cox. 1955.

Clinical Neurosurgery, Vol. I. Proceedings of the Congress of Neurological Surgeons, New Orleans, La. (Pp. viii + 202. 61*s*. 6*d*.) London : Baillière, Tindall and Cox. 1955.

The Interpretation of Dreams. By Sigmund Freud. An entirely new translation by James Strachey. (Pp. xxxii + 692. 21*s*.) London : George Allen and Unwin. 1955.

Psychotherapeutic Intervention in Schizophrenia. By Lewis B. Hill. (Pp. vii + 216. 37*s*. 6*d*.) London : Cambridge University Press. 1955.

The Work of the Mental Nurse. Manchester Mental Nursing Survey. (Pp. x + 154. 10*s*.) Manchester University Press. 1955.

Homosexuality. By D. J. West. (Pp. xiii + 145. 15*s*.) London : Gerald Duckworth. 1955.

An Introduction to Psychiatry. By Max Valentine. (Pp. viii + 15 sections + appendix and index. 15*s*.) Edinburgh and London : E. & S. Livingstone. 1955.